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Report of the National Lipid Association’s Safety Task Force: The Nonstatins

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This supplement is based in part on a workshop held February 9-10, 2006, in San Antonio, Texas, and subsequent teleconferences involving members of the National Lipid Association’s Safety Task Force and invited guests and consultants. The collection and analysis of nonstatin safety information and the publication of the Task Force’s conclusions and recommendations were supported by unrestricted educational grants from Abbott Laboratories, AstraZeneca LP, Kos Pharmaceuticals, Inc., Merck/Schering-Plough Pharmaceuticals, and Daiichi Sankyo, Inc. Editorial support was provided by Conexus Health, Inc., Tampa, Florida.
The opinions expressed in this supplement are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.
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Peter P. Toth, MD, PhD, has received speaker honorarium from AstraZeneca, Kos Pharmaceuticals, Inc., Merck & Co., Inc., Pfizer Inc, Schering-Plough Corporation and has served as a consultant to GlaxoSmithKline, Merck/Schering-Plough Pharmaceuticals, and Pfizer Inc.
We are fortunate that the currently available lipid-altering drugs have proved remarkably effective in reducing the risk for future coronary artery disease events and strokes. More than 30 major randomized, placebo-controlled clinical trials conducted over the past 2 decades have clearly established this. We are also fortunate that these drugs are very safe. In fact, for every serious adverse event encountered with 1 of these drugs, thousands of patients benefit from significant reductions in the risk for major cardiovascular (CV) events. To deploy these therapies in a manner that maximizes their benefit, health professionals need to have a thorough understanding of potential adverse effects and know how to minimize their impact. This supplement to *The American Journal of Cardiology* is provided to help health professionals meet this goal.

The National Lipid Association (NLA) assembled the Safety Task Force to conduct a rigorous, scholarly, up-to-date, and unbiased assessment of the safety of lipid-altering therapies and to summarize its findings in a leading medical journal. The first phase of its work, addressing the safety of statins, was published by the task force in a supplement to *The American Journal of Cardiology* on April 17, 2006. The second phase of its assessment, focusing on fibrates, nicotinic acid (niacin), bile acid sequestrants, cholesterol absorption inhibitors, and omega-3 fatty acids, is presented in this supplement. The members of the task force are Dr. James M. McKenney (chair, Virginia Commonwealth University, Richmond, VA), Dr. Harold E. Bays (Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY), Dr. Michael H. Davidson (Rush University Medical Center, Chicago, IL), John R. Guyton (Duke University Medical Center, Durham, NC), and Dr. Terry A. Jacobson (Emory University, Atlanta, GA).

The Safety Task Force carried out phase 2 of its assignment by first shaping questions, answerable with a yes or no, that addressed key potential adverse effects that may be encountered with these therapies. These questions addressed relatively common as well as rare, but important, adverse events. No attempt was made to carry out a comprehensive survey of all potential adverse effects associated with the target drugs. Task force members reviewed and debated the wisdom of including each question in the assessment and ultimately agreed to the questions that are included in this supplement. Each task force member was assigned ≥1 question to answer by carrying out a comprehensive study of the available published research, seeking the guidance and advice of consultants as necessary, summarizing the evidence applicable to each question and the rationale for the answer, and formulating recommendations that emanated from this evidence for health professionals to use in deploying lipid-altering drug therapies for CV risk reduction. Each task force member presented his or her findings to other task force members and to consultants, Dr. Annemarie Armani (Imprint Science, New York, NY) and Dr. Neil J. Stone (Northwestern University Feinberg School of Medicine, Chicago, IL) during a workshop so that the completeness of the identified evidence could be verified, the rationales for answers debated, and a list of recommendations to health professionals agreed to.

Independent critical reviews of selected questions and rationales were provided by the following experts, to whom we are indebted: Dr. Jacques Genest (McGill University Health Center, Montreal, Quebec, Canada), Dr. Douglas M. Heuman (Virginia Commonwealth University), Dr. Bertram L. Kasiske (University of Minnesota, Minneapolis, MN), Dr. Frank M. Sacks (Harvard School of Public Health, Boston, MA), Dr. Paul D. Thompson (University of Connecticut, Farmington, CT). Additionally, all questions pertaining to particular drug categories (eg, fibrates, nicotinic acid, omega-3 fatty acids, and gastrointestinally active drugs) were sent to recognized experts, who were invited to review these reports and craft independent expert commentaries on the subject. We are indebted to these experts—Dr. W. Virgil Brown (Emory University School of Medicine)
on fibrates, Dr. B. Greg Brown (University of Washington School of Medicine, Seattle, WA) on niacin, Dr. William S. Harris (Sanford School of Medicine of the University of South Dakota, Sioux Falls, SD) on omega-3 fatty acids, and Dr. Peter P. Toth (Sterling Rock Falls Clinic, Sterling, IL) on gastrointestinal active lipid-altering drugs—and for their fine contributions to this publication.

All drugs have the potential to cause adverse effects. Fortunately, those used to alter lipid levels and reduce CV risk are generally very safe, as reported in many randomized clinical trials and surveillance programs of the millions of patients who have taken these drugs over the past 2 decades. Even with these assurances of safety, health professionals must be ever diligent in using these drugs and remain mindful of approaches to limit the risk for adverse outcomes. This includes being knowledgeable about potential adverse effects, a recommendation with which we hope the information contained in this supplement will help. It means using the right doses and titration schedules and closely monitoring patients’ responses to therapies. It means carefully selecting patients to receive these therapies, limiting concurrent therapies with adverse interaction potential, and withholding or discontinuing drugs when appropriate. While maintaining a healthy respect for the potential for adverse effects associated with these therapies, we should also be comforted to know, as affirmed in this supplement, that lipid-lowering drug therapies are very safe and highly effective at reducing CV risk. This supports the conclusion of the Safety Task Force: it is the disease, atherosclerosis, and its consequences that should be our primary concern, and not the adverse effects associated with lipid-altering therapies.

Safety Considerations with Fibrate Therapy

Michael H. Davidson, MD, Annemarie Armani, MD, James M. McKenney, PharmD, and Terry A. Jacobson, MD

Fibrates are an important class of drugs for the management of dyslipidemia. This class of drugs is generally well tolerated but is infrequently associated with several safety issues. Fibrates, most likely by an effect mediated by peroxisome proliferator-activated receptor-α, may reversibly increase creatinine and homocysteine but are not associated with an increased risk for renal failure in clinical trials. Fibrates are associated with a slightly increased risk (<1.0%) for myopathy, cholelithiasis, and venous thrombosis. In clinical trials, patients without elevated triglycerides and/or low high-density lipoprotein cholesterol (HDL) levels, fibrates are associated with an increase in noncardiovascular mortality. In combination with statins, gemfibrozil generally should be avoided. The preferred option is fenofibrate, which is not associated with an inhibition of statin metabolism. Clinicians are advised to measure serum creatinine before fibrate use and adjust the dose accordingly for renal impairment. Routine monitoring of creatinine is not required, but if a patient has a clinically important increase in creatinine, and other potential causes of creatinine increase have been excluded, consideration should be given to discontinuing fibrate therapy or reducing the dose. © 2007 Elsevier Inc. All rights reserved.

Can Therapy with a Fibrate Result in an Increase in Serum Creatinine?

Response: Yes.

Confidence/level of evidence: 2A (Table 1).

Rationale: A reversible increase in creatinine has been noted in clinical trials with fenofibrate and has been reported with other fibrates, such as bezafibrate, ciprofibrate, and, less commonly, gemfibrozil1–14 (Table 2).4,15–20 In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, the average creatinine elevation was 12% (from 0.88 to 0.99 mg/dL), which was reversible once fenofibrate was discontinued.18 It has been proposed that fibrates, such as fenofibrate, ciprofibrate, and bezafibrate, may impair the generation of vasodilatory prostaglandins, probably because of their activation of peroxisome proliferators-activated receptors (PPARs),21 which might contribute to renal function impairment. The exact association between PPAR agonists and renal function is still unclear. Of current interest, tesaglitazar, a dual-PPAR (PPAR-α and PPAR-γ) agonist in phase 3 development for the treatment of glucose and lipid abnormalities in patients with type 2 diabetes mellitus, has most recently been withdrawn from development because of its impairment of renal function. Although this remains to be further established with fibrates, it would explain the lesser effect of gemfibrozil to increase creatinine, which fails to bind and activate PPARs to the same extent.2,7,22,23

Some investigators have observed that fibrates, as PPAR-α agonists, increase creatinine production with no attenuation of the glomerular filtration rate (GFR). In a study of 13 patients with normal or mild-to-moderate kidney disease, fenofibrate increased serum creatinine, with no significant change in directly measured GFR using inulin or creatinine clearance.4,24 The investigators postulated that the increase in serum creatinine level may reflect an induced elevation of the metabolic production rate of creatinine.

In conclusion, fenofibrate and other fibrates are infrequently associated with a moderate increase in creatinine, which is reportedly associated with an increase in creatinine production, but a reversible decrease in the GFR is also a possible mechanism of action. Therefore, if creatinine levels are significantly elevated with fibrate therapy, and no other clinically relevant cause is evident, then interruption of therapy may be warranted. In addition, more careful monitoring of creatinine levels is indicated if fibrates are used concomitantly with drugs that require dose adjustments in patients with impaired renal function (eg, metformin).

Does This Change in Serum Creatinine with Fibrates Represent Renal Damage?

Response: No.

Confidence/level of evidence: 2A (Table 1).

Rationale: Various studies have reported “renal dysfunction” associated with fibrates, but they in fact refer simply to the observed elevations in serum creatinine or...
sometimes urea levels only. Of the various clinical trials\textsuperscript{4,15,16,18,19} that have evaluated the renal effects of fenofibrate, creatinine clearance has not been reported to be decreased despite increased serum creatinine levels (Table 2). Even as urea, cystatin C, and homocysteine\textsuperscript{25–28} all increase collectively with creatinine after fenofibrate therapy, indicative of an expected reduction in the GFR, studies have failed to show any such change in the GFR.\textsuperscript{4,17,24} There were no reports of renal failure with gemfibrozil in the Helsinki Heart Study (HHS)\textsuperscript{29} or the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) study.\textsuperscript{30} Renal failure occurred in patients receiving fenofibrate in the FIELD trial, but less frequently than in those receiving placebo (T. Keech, personal communication, February 9, 2007). Moreover, despite the observed increases in creatinine in FIELD and in the Diabetes Atherosclerosis Intervention Study (DAIS) trial, fenofibrate in fact reduced progression from normal albumin excretion to microalbuminuria in these diabetes studies,\textsuperscript{18,19} which is particularly optimal in these patients as an important risk factor in the progression of diabetes to heart disease.

However, there does exist a case report of fenofibrate-associated reversible acute dysfunction in 3 renal transplant recipients,\textsuperscript{31} in whom biopsies were performed and in whom evidence suggested “possible tubular toxicity,” including predilection for injury to the proximal tubule with preservation of the basement membrane, the absence of substantial interstitial inflammation, and the absence of findings consistent with ischemic injury; all of this resolved upon discontinuation of the drug, with creatinine levels that returned to baseline. Further studies are needed to establish the pathogenetic mechanism and consequences of this fibrate-induced increase in serum creatinine levels.

Table 1

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confidence</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Very confident</td>
</tr>
<tr>
<td>2</td>
<td>Confident</td>
</tr>
<tr>
<td>3</td>
<td>Marginally confident</td>
</tr>
<tr>
<td>4</td>
<td>Not confident</td>
</tr>
<tr>
<td><strong>Type of evidence</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Well-designed RCTs, including RCTs conducted in patients who have reported adverse experiences</td>
</tr>
<tr>
<td>B</td>
<td>Single RCT with a highly statistically significant result</td>
</tr>
<tr>
<td></td>
<td>Well-conducted retrospective case-control studies with adverse experiences as primary end points</td>
</tr>
<tr>
<td></td>
<td>Managed care claims database analysis with a highly statistically significant result</td>
</tr>
<tr>
<td>C</td>
<td>Reports to regulatory agencies judged to exceed population averages and reporting bias</td>
</tr>
<tr>
<td></td>
<td>Multiple case studies with nonblinded dechallenge and rechallenge</td>
</tr>
<tr>
<td></td>
<td>Strong trends, not reaching statistical significance, for safety issues in large RCTs</td>
</tr>
<tr>
<td></td>
<td>Well-conducted prospective cohort study, giving a result that is statistically well above population average</td>
</tr>
<tr>
<td></td>
<td>Metabolic or clinical surrogate studies</td>
</tr>
<tr>
<td>D</td>
<td>Undocumented opinion of experienced research investigators and clinicians</td>
</tr>
<tr>
<td></td>
<td>Poorly controlled or uncontrolled studies</td>
</tr>
<tr>
<td></td>
<td>Nondefinitive evidence from regulatory agency reporting systems or managed care claims databases</td>
</tr>
<tr>
<td>U</td>
<td>Unknown, no appropriate evidence, or evidence considered subject to bias</td>
</tr>
</tbody>
</table>

RCT = randomized controlled clinical trial.

\* Support for evidence for or against the contention that a potential human adverse experience is related to lipid-modifying medications.
### Table 2
Effects of fenofibrate on parameters of renal function in prospective studies

<table>
<thead>
<tr>
<th>Renal Parameter</th>
<th>Study</th>
<th>DAIS 19,¶</th>
<th>Hottelart et al 4,*</th>
<th>Levin et al 15,†</th>
<th>Deighan et al 16,‡</th>
<th>Dalton et al 17,§</th>
<th>FIELD 18,∥/H11002</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR, measured CrCl</td>
<td>Unchanged</td>
<td>−8% (p = NS)</td>
<td>Unchanged</td>
<td>−3.2% (p = NS)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Inulin clearance</td>
<td>Unchanged</td>
<td>NA</td>
<td>NA</td>
<td>−2.3% (p = NS)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine % change</td>
<td>+15% (p &lt; 0.0001)</td>
<td>+27% (p = NS)</td>
<td>+14% (p &lt; 0.01)</td>
<td>+8.3%</td>
<td>+12% (0.88–0.99 mg/dL)</td>
<td>+15% (0.97–1.12 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>PAH clearance</td>
<td>Unchanged</td>
<td>NA</td>
<td>NA</td>
<td>−9%</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Creatininuria % change</td>
<td>+12% (p = 0.001)</td>
<td>NA</td>
<td>NA</td>
<td>+28%</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>NA</td>
<td>−23%</td>
<td>−2% (p = NS)</td>
<td>NA</td>
<td>NA</td>
<td>−55% (microalbumin)</td>
<td></td>
</tr>
<tr>
<td>BUN % change</td>
<td>13% (p = 0.006)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; CrCl = creatinine clearance; DAIS = Diabetes Atherosclerosis Intervention Study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; GFR = glomerular filtration rate; NA = not available; PAH = para-aminohippuric acid.

* N = 26, dyslipidemia, mild renal insufficiency, CrCl = 68 mL/min, fenofibrate 200 mg/day or every other day for 2 weeks.
† N = 28, dyslipidemia, moderate renal insufficiency, CrCl = 46 mL/min/1.73 m², fenofibrate 67–201 mg/day, 6 months, double-blind, randomized, placebo controlled.
‡ N = 12, nephrotic range, proteinuria, crossover, randomized, fenofibrate 200 mg or cerivastatin 0.2 mg for 8 weeks.
§ N = 24, healthy, 2-way 6-week crossover, double-blind, randomized, placebo controlled, fenofibrate 160 mg/day.
¶ N = 9,795, type 2 diabetes, 6-week run-in, fenofibrate 200 mg/day.
∥ N = 418, type 2 diabetes, fenofibrate 200 mg for 3 years, double-blind, randomized, placebo controlled.

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Rationale: Fibrates should be used with caution and at lower doses in patients with renal dysfunction. Fibrates should not be used in patients receiving renal dialysis.

**Should Precautions Be Taken with the Use of Fibrates in Patients with Renal Disease? What Precautions Should Be Taken?**

**Response:** Yes.

**Class Effect?**

**Confidence/level of evidence:** 3B (Table 1).

**Rationale:** Small retrospective studies have suggested that fenofibrate, bezafibrate, and ciprofibrate are more likely than gemfibrozil to increase creatinine and homocysteine levels. 4 Gemfibrozil was previously thought not to cause increased serum creatinine, but case reports and data from VA-HIT suggest that gemfibrozil is not entirely exempt.

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Avoiding it altogether when the GFR is <60 mL/min/1.73 m² (Table 3). Hence, the recommendation is that the doses of all fibrates be minimized if the GFR is <15 mL/min/1.73 m² and that fenofibrate be avoided if the GFR is <15 mL/min/1.73 m². The NKF recommends 15–59 mL/min/1.73 m², and that fibrates be used in stage 5 chronic kidney disease when the need for pharmacological modification for decreased kidney function is not severe. 3B (Table 1).
Do Fibrates Cause Cholelithiasis, Cholecystectomy, and/or Other Manifestations of Gallbladder Disease? Is This a Class Effect?

Response: Yes.

Confidence/level of evidence: 2A (Table 1).

Rationale: All fibrates appear to have the propensity to cause gallbladder disease. However, it is difficult to determine how much may be related to fibrates and how much to other causes. Risk factors for gallbladder disease are also risk factors for coronary artery disease (CAD). Thus, the very population of subjects who are candidates for CAD prevention and fibrate therapy are at higher risk for developing cholelithiasis than the general population. Differentiating between cholelithiasis that develops because of the associated risk factors and that which is caused by fibrate therapy is nearly impossible. Another issue blurring the link between fibrate therapy and gallbladder disease is that gallstones are asymptomatic. The presence of gallstones can be assessed accurately only by use of imaging, such as ultrasound. However, ultrasound surveillance is rarely used in most prospective, randomized therapeutic trials, making it difficult to assess the cholelithogenic effect of hypolipidemic drugs. Nevertheless, the evidence suggests that fibrates are lithogenic. Lines of evidence include (1) physiologic studies in humans and experimental animals demonstrating increased biliary cholesterol saturation during short-term fibrate treatment, (2) prevalence studies in patients treated chronically with different hypolipidemic agents, and (3) incidence of cholecystectomy in randomized, placebo-controlled clinical trials involving fibrate drugs.

The most important factor determining predisposition to gallstones is the concentration of cholesterol in bile relative to phospholipid and bile salt. This is commonly expressed in terms of a cholesterol saturation index, with values >1 indicating supersaturation. All of the fibrates have been subjected to bile composition analyses and show supersaturation of cholesterol in bile. In 1 study, clofibrate 2 g/day was taken by 16 patients with hyperlipidemia for 2 years.\textsuperscript{37} The cholesterol saturation index was increased by 150\% from baseline values. Six-month and 2-year data were approximately the same, suggesting that the effect did not dissipate with time. In a similar study, 8 normal male volunteers were given gemfibrozil for 3 months. The average lithogenic (cholesterol saturation) index of the bile increased from 0.73 at baseline to 1.37 (p < 0.05) after 3 months. This was due mainly to an increase in biliary cholesterol from 47 to 70 mg/day (p < 0.01) and a decrease in bile acids from 943 to 694 mg/hr (p < 0.001).\textsuperscript{38} In an attempt to determine whether the risk for cholelithiasis was different between clofibrate and gemfibrozil, 10 normal volunteers received gemfibrozil or clofibrate for 4 weeks, followed by a 4-week washout period, and the other therapy for a final 4 weeks. The cholesterol saturation index increased from 1.226 to 1.547 with clofibrate (p < 0.05) and to 1.352 (p = NS) with gemfibrozil.\textsuperscript{39} Fenofibrate therapy has been studied in a similar fashion. In 1 study, 9 patients with familial hypercholesterolemia or combined hyperlipidemia were administered fenofibrate for 4 weeks. The hepatic
secretion of cholesterol into the bile increased from 62 to 71 mg/hr, with no change in bile acid or phospholipid secretion, which resulted in an increase in cholesterol saturation from 152% to 173%.41 In a second study, 16 patients with hyperlipidemia were found to have an increase in the cholesterol saturation index from 1.25 to 1.80 (p < 0.01) with fenofibrate therapy, due to an increase in the molar percentage of cholesterol and reduction in the molar percentage of bile acids.41 A concomitant increase in phospholipids content has been described, which could minimize the increase in the cholesterol saturation index. In summary, these studies demonstrate that each of these fibrates produces a significant increase in the biliary cholesterol saturation index, primarily by stimulating increased biliary secretion of cholesterol. Indeed, this may be a major mechanism for fibrates' hypolipidemic effect. The increase in biliary cholesterol saturation appears most marked with clofibrate and fenofibrate.

Epidemiologic studies have been used to examine the incidence of gallbladder disease with fibrate therapy. In 1 study, 1,754 men and women aged ≥30 years underwent medical histories and sonographic examinations to characterize the presence of cholelithiasis.42 The frequency of fibrate use in subjects found not to have gallstones was 11.3%, compared with 20.8% in subjects with gallstones. Fenofibrate was the fibrate taken by 80% of the subjects, bezafibrate by 15%, and ciprofibrate by 5%. The 3 prominent risk factors for gallstones by multivariant analysis were age (>50 years), sex (female), and fibrate therapy. The relative risk for cholelithiasis in patients treated with fibrates was 1.7-fold (p = 0.004).

Arguably, the best way to document the association between fibrate therapy and cholelithiasis is through the analysis of clinical trials involving large groups of patients who have been randomly assigned to fibrate or placebo treatment and who can be followed over a long period. An analysis of 8 trials meeting these criteria, leads to equivocal conclusions (Table 4).18,29,30,43–47 The association of clofibrate and cholelithiasis is most clear. In the World Health Organization (WHO) Co-operative Trial45 and Coronary Drug Project (CDP),47 cholecystectomies occurred 2 to 3 times more often in subjects receiving clofibrate therapy than in placebo-treated patients. Further, the presence of biliary disease was higher in clofibrate-treated patients. Whether gemfibrozil or fenofibrate causes gallbladder disease is not clear. No cholecystectomies were not reported in the very large FIELD trial18 (in which fenofibrate was compared with placebo) or in the HHS29 or VA-HIT30 study (in which gemfibrozil was compared with placebo); there were no reports of biliary disease in any of these studies (Table 4). One assumes that if these events were not reported in the study reports, they did not occur significantly more with treatment, but it is also possible that they were not reported because they occurred infrequently or were not

### Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n (Placebo/Drug)</th>
<th>Drug</th>
<th>Duration (yr)</th>
<th>Cholecystectomies (Drug vs Placebo)</th>
<th>Biliary Disease (Drug vs Placebo)</th>
<th>GI Symptoms (Drug vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIELD18</td>
<td>9,795 (4,900/4,895)</td>
<td>Fenofibrate</td>
<td>5</td>
<td>Not reported</td>
<td>Pancreatitis 0.8% vs 0.5%</td>
<td>NR</td>
</tr>
<tr>
<td>DAIS43</td>
<td>731 (211/207)</td>
<td>Fenofibrate</td>
<td>3</td>
<td>0.5% vs 1.4%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HHS29</td>
<td>4,081 (1,587/637)</td>
<td>Gemfibrozil</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>Abdominal pain 0.5% vs 0.6%</td>
</tr>
<tr>
<td>LOCAT44</td>
<td>395 (198/197)</td>
<td>Gemfibrozil</td>
<td>2.7</td>
<td>NR</td>
<td>NR</td>
<td>New or worsening GI disease 11.2% vs 5.6%</td>
</tr>
<tr>
<td>VA-HIT30</td>
<td>2,531 (1,267/1,264)</td>
<td>Gemfibrozil</td>
<td>5.1</td>
<td>Abdominal surgery 5.4% vs 4.3%</td>
<td>7% vs 7%</td>
<td>Dyspepsia 40% vs 34%</td>
</tr>
<tr>
<td>WHO study45</td>
<td>10,627 (5,296/5,331)</td>
<td>Clofibrate</td>
<td>5.3</td>
<td>1.1% vs 0.5% (3 deaths due to cholecystectomy vs 0 with placebo)</td>
<td>NR</td>
<td>Withdrawals due to liver and gallbladder symptoms 0.5% vs 0.4%</td>
</tr>
<tr>
<td>Stockholm Ischemic Heart Disease Secondary Prevention Study46 CDP47</td>
<td>555 (276/279)</td>
<td>Clofibrate plus niacin</td>
<td>5</td>
<td>NR</td>
<td>1.8% vs 0%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>3,892 (1,587/637)</td>
<td>Clofibrate</td>
<td>5</td>
<td>4.2% vs 1.3%</td>
<td>3.3% vs 2.0%</td>
<td>Stomach pain 8.9% vs 7.9%</td>
</tr>
</tbody>
</table>

CDP = Coronary Drug Project; DAIS = Diabetes Atherosclerosis Intervention Study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; GI = gastrointestinal; HHS = Helsinki Heart Study; LOCAT = Lopid Coronary Angiography Trial; NR = not reported; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; WHO = World Health Organization.
considered important. Whatever the case, one is left with the impression that clofibrate does increase the risk for cholelithiasis and choledochocholangitis in patients but that gemfibrozil and fenofibrate, although they increase the lithogenicity of the bile, do not produce an important, detectable increase in cholelithiasis in several thousand patient-years of observation in well-controlled, randomized clinical trials. When treating patients for CAD risk reduction with fibrate therapy, the selection of either gemfibrozil or fenofibrate is preferred because of an apparent lesser risk for gallbladder problems than with clofibrate.

Even less is known with certainty about the cholelithogenic effect of fibrates when given in combination with other cholesterol-lowering drugs. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), which block hepatic cholesterol synthesis, may reduce biliary cholesterol secretion slightly, but their effects have not been consistent.

**Does the Risk for Cholelithiasis Increase When a Cholesterol Absorption Inhibitor Is Given with a Fibrate?**

**Response:** No.

**Confidence/level of evidence:** 3D (Table 1).

**Rationale:** Inhibitors of intestinal cholesterol absorption such as ezetimibe would be expected to lead to reduced cholesterol delivery to the liver, resulting in compensatory changes including the upregulation of hepatic low-density lipoprotein uptake and the upregulation of endogenous cholesterol biosynthesis. The net effect on biliary cholesterol secretion cannot be readily predicted. An international search of published research revealed little information regarding the effects of ezetimibe on human bile lipid composition or gallstone prevalence. The situation is further complicated because ezetimibe and its glucuronide metabolite also are secreted into bile and undergo enterohepatic circulation. Ezetimibe has been reported to reduce cholesterol absorption by 54%, increase the fecal excretion of neutral sterols by 72%, increase total hepatic cholesterol synthesis by 89%, and increase bile acid synthesis by a nonsignificant 17%. One-month studies of ezetimibe 0.03 to 300 mg/day in dogs found that cholesterol concentration in gallbladder bile rose 2- to 4-fold but after 1 year did not result in gallstone formation. Similar studies of bile from patients administering the fibrate-ezetimibe combination have not been conducted. Recently, a 48-week study of 576 patients with mixed hyperlipidemia compared treatment with fenofibrate 160 mg plus ezetimibe 10 mg with treatment with fenofibrate 160 mg plus placebo. The study results reported 1 planned or performed cholecystectomy in the 236 patients receiving fenofibrate alone (0.4%), compared with 4 planned or performed cholecystectomies in the 340 patients receiving the combination (1.2%). Although the data between these groups were not statistically different, a study involving a much larger group of patients may have reached significance. This study supported a recent change to the ezetimibe prescribing information as follows: “co-administration of ezetimibe with fibrates, other than fenofibrate, is not recommended until use in patients has been studied.” If the combination is being considered in a patient with a high risk for cholelithiasis or in whom cholelithiasis is suspected, it would be appropriate to carry out a definitive evaluation of the patient before starting the fibrate-cholesterol absorption inhibitor therapy.

**Do Rhabdomyolysis, Myopathy, Myalgias, and/or Creatine Kinase Elevations Occur in Patients Administered Fibrate Therapy?**

**Response:** Yes.

**Confidence/level of evidence:** 2A (Table 1).

**Rationale:** Fibrates, as monotherapy as well as combination therapy, have been reported to cause myopathy. It is the most serious safety risk associated with fibrates, although it is rare. Epidemiologic studies have estimated the incidence of myopathy associated with all lipid-lowering drugs at 2.3/10,000 person-years of treatment, with fibrate use as monotherapy confering a 5.5-fold increased risk compared with statin use, despite the low absolute risk with both classes of agents. Although infrequent, the failure to discontinue drug therapy when it occurs can result in rhabdomyolysis, leading to possible kidney failure and death. In 1 study, the number needed to treat to cause 1 case of rhabdomyolysis in 1 year with fibrate monotherapy was 3,546 patients. The risk appears to be increased for patients with diabetes, renal failure, and hypothyroidism and in older patients. Studies suggest that the mechanism of myotoxicity through fibrates is not entirely clear, because complex and multifactorial mechanisms are involved, including genetic predisposition, pharmacokinetics, drug interactions, and dose. Hypotheses suggest that fibrates may only exacerbate latent preexisting mitochondrial myopathies or accelerate the normal physiologic changes in skeletal muscle associated with aging. Fibrates may have direct toxic action on muscle cells in patients with unrecognized predispositions to myopathy.

**Do Muscle Adverse Events Occur with All Marketed Fibrates?**

**Response:** Yes.

**Confidence/level of evidence:** 3B (Table 1).

**Rationale:** Myopathy is seen with both gemfibrozil and fenofibrate, but more frequently with gemfibrozil. Of adverse events reported to the US Food and Drug Administration (FDA), rates of muscle symptoms without rhabdomyolysis were higher for gemfibrozil compared with fenofibrate, at 15.7
per million prescriptions compared with 8.8 per million prescriptions. Likewise, rates of rhabdomyolysis were significantly higher with gemfibrozil compared with fenofibrate, at 59.6 per million gemfibrozil prescriptions compared with 5.5 per million fenofibrate prescriptions.62

Do Muscle Adverse Events Occur More Frequently When a Fibrate Is Used with a Statin?

Response: Yes (for gemfibrozil).

Confidence/level of evidence: 2A (Table 1).

Rationale: The increased potential risk for myopathy and rhabdomyolysis with statin-fibrate combination therapy was first reported in 1990 with the combination of gemfibrozil and lovastatin,59 leading to changes in prescribing information for all statins, including cautionary notes implying that the benefits of the combination therapy should outweigh the increased risk for myopathy. In later years, cerivastatin, in combination with gemfibrozil, was associated with >4,000 times the rate of rhabdomyolysis compared with statin therapy alone, and numerous fatalities63 were reported, resulting in the removal of cerivastatin from the worldwide market. It was estimated that cerivastatin, in combination with gemfibrozil, required hospitalization for rhabdomyolysis in ≥1 in 10 patients.53 Nevertheless, there were no cases of myopathy or rhabdomyolysis in the patients treated with the combination of simvastatin and fenofibrate in Effectiveness and Tolerability of Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (SAFARI)64 and the combination of cerivastatin and fenofibrate in the discontinued Lipid in Diabetes Study (LDS).65 When the LDS trial was canceled (when cerivastatin was withdrawn from the market), there were >2,000 patients receiving the combination therapy.

After cerivastatin, there is still a clinically significant difference in safety with the combination of fibrates and statins. For example, in a summary of the clinical trial experience of 4,200 patients taking lovastatin, the rate of myopathy was 0.4% overall. Among 80 patients taking lovastatin and gemfibrozil, however, the frequency increased to 5%.66 Another study described a 20- to 30-fold increase in creatine kinase levels associated with statin-fibrate combination therapy compared with the individual use of these agents.67 This is particularly true with gemfibrozil-statins.68,69 (Table 7). Recent reviews of the FDA’s Adverse Events Reporting System database estimated the rate of myopathy for gemfibrozil with a statin to be 33 times more than that of a statin with fenofibrate.62,69 In the recent longer-term FIELD trial (5-year follow-up), approximately 1,000 patients were receiving fenofibrate and a statin, with no cases of rhabdomyolysis reported with the...
combination. Patients taking statin-fibrate combinations have developed rhabdomyolysis after switching from 1 fibrate and/or statin to another, including from pravastatin-fenofibrate to simvastatin-gemfibrozil and from pravastatin-gemfibrozil to simvastatin-gemfibrozil. Interestingly, rhabdomyolysis has also been reported after switching from gemfibrozil to bezafibrate monotherapy.

The reason for the much greater propensity for gemfibrozil to increase the risk for myopathy with a statin is most likely the difference in the pharmacokinetic interactions between the 2 fibrates (Table 8). Gemfibrozil can increase the plasma concentrations of cerivastatin, simvastatin, lovastatin, pravastatin, atorvastatin, and rosuvastatin with the most marked impact on cerivastatin and the least effect on fluvastatin. Although lipophilic statins are hydrolyzed by the cytochrome P450 (CYP) enzymes to increase water solubility for renal excretion, statins are also metabolized by glucuronidation. Gemfibrozil uses the same family of glucuronidation enzymes as the statins, thereby inhibiting statin acid glucuronidation. The half-maximal inhibitory concentrations for the inhibition of the glucuronidation of simvastatin hydroxy acid, atorvastatin, rosuvastatin, and cerivastatin are 354, 316, 400, and 82 mol/L, respectively. Because the half-maximal inhibitory concentrations are comparable to gemfibrozil’s peak plasma concentrations, these data suggest that these statins, particularly cerivastatin, may be susceptible to the inhibition of glucuronidation when administered with gemfibrozil. Another gemfibrozil-mediated pathway, contributing to an increase in statin concentrations and the risk for skeletal muscle injury, involves the inhibition of CYP 2C8 activity. The more prominent increase in the area under the curve for gemfibrozil and cerivastatin may be due to the effect of CYP 2C8 and to glucuronidation. Rosiglitazone and repaglinide are also CYP 2C8 metabolized, and blood levels have also been shown to increase in combination with gemfibrozil, but not with fenofibrate. Therefore, in patients with diabetes, combination therapy with fenofibrate appears to be the most appropriate fibrate choice. Because gemfibrozil does not adversely affect fluvastatin pharmacokinetics, alternatively, if gemfibrozil is necessary, fluvastatin may be an appropriate statin option to consider for combination with gemfibrozil. Risk factors for myopathy associated with statin-fibrate therapy include increased age, female sex, renal or liver disease, diabetes, hypothyroidism, debilitation, surgery, trauma, excessive alcohol intake, and heavy exercise.

Although less studied, fenofibrate has not been reported to alter the pharmacokinetics of statins significantly. Gemfibrozil uses the same family of glucuronidation enzymes as statins, fenofibrate uses a different enzyme family. Fenofibrate has been shown to have little effect on the pharmacokinetics of pravastatin, rosuvastatin, simvastatin, or atorvastatin. This lack of a pharmacokinetic interaction between statins and fenofibrate relaxed the recommendation in the package inserts for simvastatin, fluvastatin, and rosuvastatin, allowing all doses to be used in combination with fenofibrate. The recent NCEP guideline update also supports lessening the concern regarding this combination.

Hence, fenofibrate is frequently prescribed for combined dyslipidemia.

In 2000, a joint American College of Cardiology (ACC)/American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) advisory committee on the use and safety of statins reviewed 8 controlled clinical trials of statin-fibrate therapy involving almost 600 patients. This review found that 1% of patients experienced creatine kinase levels >3 times the upper limit of normal without muscle symptoms, and 1% withdrew from therapy because of muscle discomfort; none of the findings were considered serious by the investigators, and no cases of rhabdomyolysis or myoglobinuria had been reported. This statin safety advisory committee concluded that the combination of a moderately dosed statin with a fibrate “appears to have a relatively low incidence of myopathy, especially when used in persons without multiple-system disease or multiple medications.”

In conclusion, in combination with a statin, fenofibrate is the preferred fibrate option. However, because fenofibrate and statins are independently associated with an increased combination. Patients taking statin-fibrate combinations have developed rhabdomyolysis after switching from 1 fibrate and/or statin to another, including from pravastatin-fenofibrate to simvastatin-gemfibrozil and from pravastatin-gemfibrozil to simvastatin-gemfibrozil. Interestingly, rhabdomyolysis has also been reported after switching from gemfibrozil to bezafibrate monotherapy.

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In conclusion, in combination with a statin, fenofibrate is the preferred fibrate option. However, because fenofibrate and statins are independently associated with an increased
risk for myopathy, to enhance the safety of fibrate-statin combination treatment, it is advisable not to use the maximal dose of a statin in combination with fenofibrate.

Does Fibrate Therapy Lead to an Increase in Cardiovascular, Noncardiovascular, and/or Total Mortality? If So, What Is the Origin of the Increased Mortality?

Response: Unknown.

Confidence/level of evidence: 3A (Table 1).

Rationale: Fibrate trials have demonstrated a significant reduction in nonfatal myocardial infarction (MI), but many trials, especially those that used clofibrate, have also noted increases in cardiovascular (CV) and total mortality. The FDA has consistently mandated a warning about mortality in every fibrate package insert, primarily because of 2 clinical trial experiences, both with clofibrate, from 30 years ago (Table 9).92–95 In the first of those studies, the CDP,47 1,000 subjects with previous MI were treated for 5 years with clofibrate. Although there was no difference in mortality between the clofibrate-treated subjects and 3,000 placebo-treated subjects, twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. Subsequently, in the WHO trial,45,93 5,000 subjects without known CAD were treated with clofibrate for 5 years and followed 1 year beyond that. There was a statistically significant 36% higher mortality rate due to non-CV causes in the clofibrate-treated group than in a comparable placebo group.45,96 The excess mortality appeared to be due to a 33% increase in non-CV causes, including gastrointestinal.

Table 8
Statin-fibrate combination therapy: pharmacokinetic interactions

<table>
<thead>
<tr>
<th>Statin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Cerivastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>↑ in C_{max}</td>
<td>2-fold ↑ in C_{max}</td>
<td>2-fold ↑ in C_{max}</td>
<td>No effect</td>
<td>2.8-fold ↑ in C_{max}</td>
<td>2–3-fold ↑ in C_{max}</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Not available</td>
</tr>
</tbody>
</table>

C_{max} = peak plasma concentration; ↑ = increase.
Adapted from J Clin Hypertens (Greenwich).73

Table 9
Fibrate trials and mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration (yr)</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Mortality</th>
<th>Fibrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDP</td>
<td>5</td>
<td>8,341</td>
<td>Clofibrate 1.8 g/day</td>
<td>CAD mortality 17.7%</td>
<td>19.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD mortality 21.8%</td>
<td>22.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mortality 25.5%</td>
<td>25.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer mortality 0.9%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>5.3 (9-yr follow-up)</td>
<td>15,745</td>
<td>Clofibrate 1.6 g/day</td>
<td>Before closure of trial⁹²</td>
<td>IHD mortality 1.7%</td>
<td>1.45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mortality 4.43%</td>
<td>3.42%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-IHD mortality 2.72%</td>
<td>1.96%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer mortality 1.4%</td>
<td>1.04%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After closure of trial⁹²</td>
<td>IHD mortality 4.07%</td>
<td>3.89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mortality 9.08%</td>
<td>8.86%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-IHD mortality 5.01%</td>
<td>4.97%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer mortality 2.45%</td>
<td>2.68%</td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td>5</td>
<td>4,081</td>
<td>Gemfibrozil 600 mg bid</td>
<td>CAD mortality 1.7%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mortality 4.9%</td>
<td>4.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer mortality 1.5%</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>FIELD</td>
<td>5</td>
<td>9,795</td>
<td>Fenofibrate 200 mg</td>
<td>CHD mortality (p = 0.22) 2.2%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV mortality (p = 0.41) 2.9%</td>
<td>2.6%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mortality (p = 0.18) 7.3%</td>
<td>6.6%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAD mortality (p = 0.07) 7.4%</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mortality (p = 0.23) 15.7%</td>
<td>17.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer mortality 3.6%</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>VA-HIT</td>
<td>5.1</td>
<td>2,531</td>
<td>Gemfibrozil 1,200 mg/day</td>
<td>CAD mortality 17.7%</td>
<td>19.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD mortality 21.8%</td>
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<td></td>
<td></td>
<td></td>
<td>Cancer mortality 0.9%</td>
<td>1.1%</td>
<td></td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CDP = Coronary Drug Project; CV = cardiovascular; CVD = CV disease; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HDL = high-density lipoprotein; HHS = Helsinki Heart Study; IHD = ischemic heart disease; MI = myocardial infarction; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; WHO = World Health Organization.

* Type 2 diabetes, total cholesterol 3.0–6.5 mmol/L, total cholesterol/HDL ≥4, triglycerides 1–5 mmol/L.
† CAD, HDL ≤40 mg/dL, low-density lipoprotein ≤140 mg/dL, triglycerides ≤300 mg/dL.
malignancies, complications after cholecystectomy, and pancreatitis. Because of the similarities in some of these underlying diagnoses common to these 2 trials, this raised concern.

During the 5-year primary prevention component of the HHS, the total mortality was similar in the gemfibrozil and placebo arms during the original 5 years but higher in the gemfibrozil group after the trial, leading to an 8.5-year mortality of 4.9%, compared with placebo at 4.1% (hazard ratio, 1.20; \( p = 0.12 \)).94 This was mainly a result of higher cancer deaths trended higher in the gemfibrozil group (n = 30 [1.5%]) compared with placebo (n = 18 [0.9%], \( p = 0.08 \)). The incidence of cancers (excluding basal-cell carcinoma) discovered during the trial and in the 3.5-year follow-up period was determined to be equal in the 2 groups. The investigators did conclude that the increased cancer and total mortality were most likely due to chance, on the basis of the later reversal of these trends in follow-up. Moreover, in the secondary prevention component of the HHS, although cardiac deaths trended higher in the gemfibrozil group, this also was not statistically significant (hazard ratio, 2.2; 95% confidence interval, 0.94–5.05).

More recently, in the FIELD trial,18 the investigators also reported a nonsignificant excess in non-CV mortality (as well as CAD mortality, CV mortality, and total mortality) associated with fenofibrate that was somewhat consistent with the earlier fibrate trials. However, this apparent excess was not attributable to any specific cause of death, such as invasive cancers, and the investigators again concluded that this remained consistent with a chance finding.

In the VA-HIT, gemfibrozil was associated with a nonsignificant 22% reduction in death from CAD (7.4% vs 9.3%; \( p = 0.07 \)), as well as a nonsignificant 11% reduction in overall mortality in this trial (\( p = 0.23 \)).30

Fibrates are recommended and are optimal therapy for patients with hypertriglyceridemia and low HDL (atherogenic dyslipidemia), and thus far, the VA-HIT remains the sole trial among these larger fibrate outcome trials actually to study this population of patients (Table 9). In the HHS, the subgroup of patients with atherogenic dyslipidemia demonstrated an improved clinical benefit compared with the entire study population. The patients taking gemfibrozil with body mass indexes and triglyceride levels in the highest tertiles had a 71% lower relative risk for CAD mortality (\( p < 0.001 \)) and a 33% lower relative risk for all-cause mortality (\( p = 0.03 \)).97 The Bezafibrate Infarction Prevention (BIP) trial56 also noted that the greatest benefit was in patients with elevated triglycerides. In the FIELD trial, the greatest absolute benefit in total CV disease events was in the one third of patients with atherogenic dyslipidemia.

In conclusion, the use of fenofibrate and gemfibrozil in patients with dyslipidemia characterized by elevated triglycerides and low HDL cholesterol in clinical trials demonstrates an improved CV benefit without unfavorable effects on atherogenic mortality. Therefore, gemfibrozil and fenofibrate, if used appropriately in the dyslipidemic population (ie, high triglycerides and low HDL cholesterol), would be expected to provide the greatest benefit–risk ratio. On the basis of clinical trial data, the use of clofibrate in the general population, or gemfibrozil and fenofibrate in patients without dyslipidemia, is not likely to demonstrate a favorable benefit–risk ratio and is therefore unwarranted.

**Is There a Concern of Cancer with Fibrate Therapy?**

**Response:** No.

**Confidence/level of evidence:** 3A (Table 1).

**Rationale:** Concern about a possible increase in cancer-related deaths arose from fibrates’ contribution to the total mortalities observed in the WHO45 and HHS94 trials (Table 9). During the “in-trial” period of the WHO study, rates of colon, gallbladder, liver, and rectal cancer deaths were doubled in the clofibrate-treated group (0.05% vs 0.021% in the control group; \( p < 0.05 \)).45 although cancer diagnoses and death rates had become equivalent between treatment groups by the time the follow-up period had concluded.92,93 In the HHS, although cancer deaths trended higher in the
Fibrate Therapy?

Is Thromboembolic Disease Associated with diagnoses or death between treatment groups.

There otherwise have been no similar reports disease in clofibrate-treated patients (5.2% vs 3.3% in the placebo group).47 There had not been previously reported with, nor were they aware of any thrombotic tendency from, fenofibrate treatment. More surprising to report a statistically significant but, again, inconsistency. (See the preceding discussion of cancer.) Nevertheless, the investigators deemed the finding as owing to chance.44 In both VA-HIT30 and FIELD,18 there were no significant increases in cancer diagnoses or death between treatment groups.

Is Thromboembolic Disease Associated with Fibrate Therapy?

Response: Yes.

Confidence/level of evidence: 3B (Table 1).

Rationale: New long-term data from the FIELD18 study demonstrated a small, but statistically significant, increased risk for venothromboembolic disease (pulmonary embolism [p = 0.022] and deep venous thrombosis [p = 0.074]) associated with treatment with fenofibrate. The investigators believed that this small increase of venothromboembolic events had not been previously reported with, nor were they aware of any thrombotic tendency from, fenofibrate treatment. More than 30 years ago, however, the investigators of the CDP were also surprised to report a statistically significant but, again, small increase in the 5-year incidence of venothromboembolic disease in clofibrate-treated patients (5.2% vs 3.3% in the placebo group).47 There have been no similar reports in the larger fibrate trials in the published research, including the WHO study,45 VA-HIT,30 and the HHS.29

Two factors conceivably associated with hypercoagulability and fibrates worthy of discussion are homocysteine and underlying malignancy. A recent meta-analysis of prospective and retrospective studies demonstrated a modest association of homocysteine with venous thrombosis.98 Treatment with fibrates, fenofibrate in particular, is well known to increase homocysteine levels.18,26–28,99–101 although the clinical significance of this is less clear. (See the following discussion of homocysteine.) Cancer is another well-established hypercoagulable state and is a leading cause of deep venous thrombosis and pulmonary embolism, and fibrates have come under question for their potential carcinogenicity. (See the preceding discussion of cancer.) Nevertheless, in both trials reporting increases in venothromboembolic events (FIELD and the CDP), there were no increased rates of cancer diagnoses or deaths.18,47 Furthermore, neoplastic manifestations such as deep venous thrombosis typically arise only when cancers are considerably advanced, so this is less likely.

Several fibrate derivatives decrease thrombogenic factors such as fibrinogen and plasminogen activator inhibitor–1 (PAI-1) levels. Fenofibrate has been shown to decrease fibrinogen and PAI-1.102–104 Gemfibrozil also decreases PAI-1 levels,105,106 and conflicting data have been reported on gemfibrozil’s effect on fibrinogen.103,107–111 Consequently, there may be a balance of opposing effects of fibrates on thrombosis (homocysteine) weighed against positive fibrinolytic effects (PAI-1 and fibrinogen). It is also known that high concentrations of PAI-1 in plasma are associated with high concentrations of triglycerides, perhaps because both are influenced by hyperinsulinemia.112–115 Hence, these potential positive “pleiotropic” effects of fibrates on fibrinolysis in this population may often overshadow possible hypercoagulability caused by homocysteine and other unidentified factors.

Is the Increase in Homocysteine with Fibrate Therapy Clinically Relevant?

Response: Uncertain.

Confidence/level of evidence: 4D (Table 1).

Discussion: Beyond a risk for hypercoagulability, increased homocysteine has been suggested to be associated with increased risk for coronary, cerebral, or peripheral vascular disease,115 and treatment with fibrates is well known to increase homocysteine levels.26–28,99–101,116 de Lorgeril and colleagues26 first reported a 46% increase in plasma homocysteine in patients who were treated with fenofibrate for 12 weeks. Other fenofibrate studies have confirmed strikingly similar results,27,28,100,101.117 whereas this appears to happen to a lesser extent, if at all, with gemfibrozil therapy28,116 (Table 10).118,119 Fenofibrate increases plasma homocysteine levels relatively rapidly; changes can be observed within 8 weeks of the initiation of the drug.101 In the DAIS trial, fenofibrate use was associated with a 55% increase in plasma homocysteine without attenuating the beneficial effects of fenofibrate on the angiographic progression of CAD or clinical events over a period of nearly 3.5 years.119 In a post-hoc analysis of the FIELD trial, in patients with the highest tertile increase in homocysteine (>4 μmol/L), there was proportionately less reduction in CVD events.119a Ultimately, whether the observed increases in homocysteine counteract the net benefit of fibrates, however, requires further study.

The mechanism of action for elevated homocysteine remains unclear because fibrates have been shown not to alter homocysteine’s principal determinants (vitamins B6 and B12 or folate status)28,101,119 or to have an effect on renal function that clearly explains the observed increase.24,100,120 Animal studies have suggested that the homocysteine level increase might be mediated by a direct PPAR-α action.121

Whether the increase in homocysteine outweighs the benefit of fenofibrate on lipids, fibrinogen, and PAI-1 still needs to be further assessed. For example, it still may be reasonable to counteract the increase of total homocysteine by the concurrent application of agents known to lower homocysteine safely and effectively, such as folate or vitamins B6 and B12. However, there is no evidence that this approach will further enhance the beneficial effect of feno-
Table 11
Recommendations to healthcare professionals regarding fibrate safety

1. Before the initiation of fibrate therapy, a measurement of serum creatinine should be determined. If impaired renal function is present, the patient should be prescribed gemfibrozil (unless taking a statin), or a lower starting dose of fenofibrate (48 mg is most commonly available) should be considered. With impaired renal function, the periodic monitoring of renal function is recommended.

2. Routine monitoring of creatinine is not required, but if a patient has a clinically important increase in creatinine, and other potential causes of creatinine increase have been excluded, consideration should be given to discontinuing fibrate therapy or reducing the dose.

3. Creatinine monitoring may be advisable if a patient is taking another medication, such as metformin, which may need to be discontinued for creatinine elevations $\geq 1.4 \text{ mg/dL}$ in women and $\geq 1.7 \text{ mg/dL}$ in men, or a statin, which may require downward dosage adjustment.

4. Although package inserts generally suggest using the combination of a fibrate and a statin very carefully or not at all, there are several circumstances in which the benefits may outweigh the risks. In these circumstances, fenofibrate is the preferred fibrate over gemfibrozil but still may increase the risk for myopathy or rhabdomyolysis. It is generally recommended to get a baseline CK level before adding the second lipid-lowering agent and to use the lowest dose of a statin or fibrate when possible.

5. Clinicians should still use caution when prescribing the highest doses of statins used in combination with fibrate therapy, because both classes of drugs are independently associated with an increased risk for myopathy. In combination with a statin, fenofibrate is the preferred option, and gemfibrozil should be avoided unless the clinical benefits outweigh the increased risk for myopathy. Clinicians should be aware of the maximal statin dose allowed in combination with gemfibrozil in the package insert.

6. Gemfibrozil has less effect than fenofibrate on creatinine and therefore is the National Kidney Foundation’s (NKF) fibrate of choice for renal insufficiency. It does seem reasonable to discourage the administration of fenofibrate to kidney transplant patients and those on dialysis, because fenofibrate is nondialysable.

7. In patients with renal dysfunction receiving statin therapy, especially statins with significant renal clearance (ie, simvastatin, rosuvastatin, pravastatin, and lovastatin), combination therapy with gemfibrozil should be avoided, and combination therapy with fenofibrate should be initiated with caution, if at all. The dose of fenofibrate should not exceed 48 mg (unless the benefits markedly outweigh the increased risk for rhabdomyolysis), and the statin doses should remain below the maximal levels.

8. Clinicians should warn patients about the possibility of myopathy on fibrate therapy and advise the reporting of side effects of diffuse muscle pain or weakness as soon as possible.

9. Obtaining a pretreatment baseline CK level may be considered in patients who are at high risk for experiencing muscle toxicity, but this is not routinely necessary in other patients.

10. It is not necessary to measure CK levels in asymptomatic patients during the course of fibrate therapy, because marked, clinically important CK elevations are relatively rare. CK measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses.

11. In patients who develop intolerable muscle symptoms with or without CK elevations, and in whom other causes have been ruled out, fibrates should be discontinued. In patients who develop rhabdomyolysis (CK $>10,000 \text{ IU/L}$ or CK $>10 \times \text{ ULN}$ with an elevation in serum creatinine or requiring IV hydration therapy), fibrate therapy should be stopped. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once recovered, the risks and benefits of fibrate therapy should be carefully monitored.

12. Clinicians should be aware that fibrates have not been demonstrated to significantly reduce total and cardiovascular mortality. On post hoc analysis, certain lipid subpopulations have been shown to have greater cardiovascular benefit (ie, elevated triglycerides and/or low HDL), but this needs to be confirmed prospectively.

13. Fibrate therapy elevates homocysteine, however, routine monitoring of plasma homocysteine levels on fibrate is not necessary unless further research ascertains that this elevation is clinically relevant.

14. Caution should be exercised when anticoagulants are given in conjunction with both fenofibrate and gemfibrozil because of the potentiation of coumarin-type anticoagulants in prolonging PT and the INR. Frequent PT and INR determinations are advisable, and coumadin doses may need to be reduced to maintain PT and the INR at the desired level to avoid bleeding complications.

15. All fibrates have the potential to increase the cholesterol saturation index and increase the risk for cholelithiasis; however, cases of gallbladder disease and cholecystectomies appear to be uncommon with gemfibrozil and fenofibrate. If cholelithiasis is suspected in a patient receiving fibrate therapy, gallbladder studies, including ultrasound, are indicated. If gallstones are found, consideration should be given to stopping fibrate treatment.

CK = creatine kinase; HDL = high-density lipoprotein; INR = international normalized ratio; IV = intravenous; PT = prothrombin time; ULN = upper limit of normal.

**Fibrate Treatment**

Furthermore, 2 trials, the Heart Outcomes Prevention Evaluation Study Extension (HOPE-2) and the Norwegian Vitamin Trial (NORVIT), recently revealed that despite the known homocysteine-CV risk association, the reduction of homocysteine levels ultimately did not improve CV morbidity or mortality.125,126

**Is There a Change in the International Normalized Ratio or Partial Thromboplastin Time When a Fibrate Is Given with Coumarin Anticoagulants?**

**Response:** Yes.

**Confidence/level of evidence:** 1A (Table 1).

**Rationale:** Caution should be exercised when anticoagulants are given in conjunction with fenofibrate and gemfibrozil because of the potentiation of coumarin-type anticoagulants in prolonging prothrombin time and increasing the international normalized ratio.127,128 Although the mechanism of these interactions is not entirely known, potential mechanisms include the displacement of warfarin from protein binding sites, an increased affinity of the anticoagulant for binding sites, altered anticoagulant metabolism (fenofibrate is a mild to moderate inhibitor of CYP 2C9),39 and/or potential drug-induced reductions in coagulation factor synthesis.128–131 A potential for an exaggerated anticoagulant effect was shown to occur within 5–10 days in patients...
treated with fenofibrate. The dosage of the anticoagulant should be reduced (eg, 25%–33% less) to maintain prothrombin time and the international normalized ratio at the desired levels to prevent bleeding complications. Frequent prothrombin time and international normalized ratio determinations (≥3 times/wk) are advisable until it has been determined that prothrombin time and the international normalized ratio have stabilized.

Final Conclusions and Recommendations

On the basis of the preceding discussion and review of evidence, recommendations to healthcare professionals regarding fibrate safety are summarized in Table 11.

Acknowledgement

The authors wish to thank Anthony Keech for his helpful comments.


47. Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360–381.


Expert Commentary: The Safety of Fibrates in Lipid-Lowering Therapy

W. Virgil Brown, MD

The use of fibrates in the management of lipoprotein disorders has a history dating back to the mid-1960s. This group of drugs has now been tested in several large long-term trials with cardiovascular end points. Overall, there is good evidence for the reduction of cardiovascular disease in primary prevention studies and in those of subjects with manifest disease. More recent trials have suffered from high interference due to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) introduction, particularly in their placebo control groups. However, there is very good evidence for overall safety from a combined study of >20,000 patients in these controlled clinical trials lasting approximately 5 years. Abdominal pain has been observed more frequently in the statin vs placebo group. Myopathy, liver enzyme elevations, and cholecystitis have been potential adverse reactions of interest. However, these have occurred at a very low rate and are rarely found to be statistically more frequent in the active-treatment group compared with the subjects taking placebo. The recent Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found a slightly higher incidence of pancreatitis, deep venous thrombosis, and pulmonary embolism. Small creatinine and homocysteine elevations are observed in many patients taking fibrates, and the effect of this on long-term outcomes is under study. The FIELD study also described a significant reduction in the rates of progression of proteinuria and vascular retinopathy with fibrate therapy. To date, there has been no study exclusive to patients with elevated triglycerides, raising the question of the potential benefit of these drugs in patients with the lipid abnormalities most effectively treated with fibrates. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:19C–21C)

Fibrates have survived as useful tools in the management of hyperlipoproteinemia for 40 years, although their major effect, lowering plasma triglyceride concentrations, has not received endorsement by regulatory agencies as an effective means of reducing vascular disease. Furthermore, their discovery was serendipitous and their use empirical, without a documented mechanism of action for most of those 4 decades. The proliferation of hepatic peroxisomes in rodents was initially thought to be a toxic effect but was ultimately found to be a manifestation of a fundamental pharmacologic mechanism of action for this class of drugs: the activation of a series of genes that affect lipid metabolism through binding to a nuclear receptor, now known as the peroxisome proliferator-activated receptor-α (PPAR-α). This receptor with its fibrate ligand acts as a copromoter or repressor (depending on the gene) in the control of the transcription of messenger RNA for apolipoproteins, lipases, lipid-oxidizing enzyme systems, and transmembrane lipid transport systems.1 The full effect of the activation of this system remains under active study.2 Ironically, the name given to the receptor, peroxysomal proliferator, seems to be a characteristic of rodents and may have no corresponding manifestation in primates.

The first fibrate, clofibrate, was discovered when its use as a vehicle for androgen administration resulted in the finding that the vehicle alone (used as a control) was as effective in reducing plasma lipids as the combination.3 Its introduction into the clinical setting provided a very effective agent for reducing high plasma triglyceride concentrations.4 Fibrates can produce significant low-density lipoprotein (LDL) cholesterol reductions of >20% in those with triglycerides in the desirable range of <150 mg/dL (1 mg/dL = 0.01129 mmol/L).5 However, in those with high triglyceride concentrations, LDL cholesterol concentrations frequently increase.6 The most dramatic effect occurs in patients with dysbetalipoproteinemia, a disorder of impaired clearance of very-low-density lipoprotein and chylomicron remnants.7,8 In these patients, tuberous xanthomas disappeared, and evidence of improved arterial flow in the lower extremities was reported.9 In the Coronary Drug Project (CDP)10 and later in a World Health Organization (WHO) study,11 clofibrate therapy in patients with histories of coronary artery disease (CAD) produced significant reductions in myocardial infarction. However, in the WHO study, total death was reported to be significantly greater with clofibrate.
treatment than with placebo. This raised widespread concern about the potential increase in mortality, even though the reduction in CAD events was confirmed. A later analysis of these data suggested that a technical defect in the study design led to biased follow-up of the clofibrate group that could have produced an artificial increase in reported deaths. A series of analogues (gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate) have been developed and have essentially replaced clofibrate in most countries. All but ciprofibrate have been tested in large, long-term, placebo-controlled clinical trials with vascular end points. These have provided a large body of safety data that are supported by clinical experience in millions of patients around the world.

The discussion of fibrate safety in this supplement provides a detailed review of the major questions that remain. At this point, it can be said that the adverse experiences of patients while taking these drugs differ little from those experienced while taking placebo. One exception appears to be the occurrence of abdominal pain. This was the only adverse effect, with gemfibrozil, that achieved statistical significance in the Helsinki Heart Study (HHS). Because bile is known to become more lithogenic with fibrate treatment, this raised the question of whether the biliary compositional change with fibrates led to cholelithiasis in humans within the 5 years of the trial. There was a statistically significant increase in the surgical removal of gallstones from clofibrate-treated patients during the CDP and the WHO study. There was a trend toward more cholecystectomies in HHS, but this did not achieve significance. However, no other study, including the much larger Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, has had a similar experience. Therefore, it remains unclear whether there is a significant risk for rapidly advancing cholelithiasis with all fibrate therapy.

Very early in the use of clofibrate, a seemingly high incidence of myopathy was reported in the United States. This was much less common in Europe, and, over time, became rare in the American experience. An increase in cardiac arrhythmias was also reported, but such reports have also disappeared from recent published research. The observation that the combination of gemfibrozil and lovastatin can lead to myopathy was made within a few months of the onset of drug therapy. It is of interest that a small increase in homocysteine was also observed in several studies that evaluated the potential effects of this change on the vascular disease rates in the FIELD study are under evaluation.

A reduction in proteinuria had previously been reported with fenofibrate in the Diabetes Atherosclerosis Intervention Study (DAIS), which contained only 400 patients; this finding was not widely recognized as significant. FIELD provided statistically significant data that, in patients with diabetes, the progression of proteinuria was reduced in the fenofibrate-treated group compared with the placebo group. The potential improvement in the course of microvascular involvement with this drug was further supported by the reduced need for laser therapy for retinopathy with the fibrate in FIELD. This raises important questions about the mechanism of action of this drug and the potential for PPAR-α activators in general to provide new and effective

The recent FIELD study provided the largest database yet with placebo control of fibrate therapy, allowing long-term observation (5 years). It should be noted that in FIELD, the higher “drop-in” rate of statin use was significantly higher in the placebo group than in those initially assigned to the fenofibrate treatment cohort, leaving some uncertainty as to the true cause of adverse events in these patients. There were several surprises from this data set. A small increase in the incidence of pancreatitis in those taking the fibrate (0.8%) compared with placebo (0.5%) did not appear to be related to severe hypertriglyceridemia, leaving open the (undocumented) possibility that cholelithiasis might be playing a role. There also were slight increases in deep venous thrombosis (1.4% vs 1.0%) and in pulmonary emboli (1.1% vs 0.7%) in patients receiving fenofibrate versus placebo, respectively. The lack of previous evidence that clotting parameters were altered by this drug may indicate that these observations are an artifact of multiple simultaneous comparisons in this data set. However, these differences in adverse event rates should prompt more in-depth assessments of thrombotic factors in future studies of fibrates and PPAR-α activators.

It has been known for many years that fenofibrate therapy leads to an increase in serum creatinine of approximately 10%–20%. This effect has been found to be reversible with discontinuation of the drug. However, this phenomena has been troubling, particularly in the management of diabetes mellitus, in which renal disease is an important complication. This increase in creatinine was confirmed in the FIELD study. This provided for a systematic follow-up in several hundred patients taken off the drug as FIELD ended. These data have now confirmed the return to baseline concentrations of serum creatinine, and there has been no direct evidence of any permanent renal damage, except in those with severe renal damage at the onset of drug therapy. It is of interest that a small increase in homocysteine was also observed in several studies, and the potential effects of this change on the vascular disease rates in the FIELD study are under evaluation.
approaches to prevent microvascular disease. This trial also provided a large but unplanned experience with combination treatment, because 17% of those patients assigned to fenofibrate had received statins as well by the end of the study. In the placebo group, ultimately 36% of the patients were given statins. The occurrence of myopathy was very uncommon in all groups, but no cases were observed in those taking the fibrate and a statin. This appears to support the previous observational evidence that this particular fibrate can be used safely in combination therapy. A large clinical trial, now in progress (Action to Control Cardiovascular Risk in Diabetes [ACCORD]), testing fenofibrate compared with placebo in simvastatin-treated patients with diabetes should add very important new data on efficacy and safety for this high-risk population. Furthermore, this trial will provide the first data from a population that has significant hypertriglyceridemia.

Fibrates have been available for lipid reduction for a very long time. The trials to date have given remarkably favorable evidence regarding their safety when used with knowledge of drug interactions and with caution in patients with organ failure (renal or hepatic). The future use of these agents needs to be guided by additional data on their effectiveness in preventing vascular disease in those with high triglycerides and low levels of high-density lipoprotein cholesterol. This is particularly true for those patients who have these lipoprotein abnormalities after treatment with statins and other drugs that produce successful reductions of elevated LDL.

Safety Considerations with Niacin Therapy

John R. Guyton, MD, a,* and Harold E. Bays, MD b

Niacin has beneficial effects on plasma lipoproteins and has demonstrated clinical benefits in reducing cardiovascular events and atherosclerosis progression. The side effects of niacin, however, have limited its use in general clinical practice. An understanding of cutaneous flushing based on the best available evidence should enhance patient education efforts and improve adherence. Although serious hepatic toxicity from niacin administration has been reported, it is largely confined to the use of slow-release formulations given as unregulated nutritional supplements. Niacin has been shown to induce insulin resistance in short-term trials, but the glycemic response in subjects with and without diabetes is usually minor. Niacin can be used safely in patients with diabetes. Despite a few case reports of myopathy associated with niacin-statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) combination therapy, 2 decades of clinical evidence since the introduction of statins do not support a general myopathic effect of niacin either alone or in combination with statins. Rare, less well-defined side effects of niacin include blurred vision due to cystoid macular edema, nausea and vomiting, and the exacerbation of peptic ulcers. Laboratory abnormalities that are usually small (≤10%) and clinically unimportant include increased prothrombin time, increased uric acid, and decreases in platelet count and serum phosphorus. Overall, the perception of niacin side effects is often greater than the reality. As a result, a valuable medication for cardiovascular risk is underused. © 2007 Elsevier Inc.

Are There Ways to Substantially Reduce the Flushing, Pruritus, and Skin Rash Side Effects Associated with Niacin Use?
Response: Yes.
Confidence/level of evidence: 1C (Table 1).

Can the Skin Rash Manifest as Hives?
Response: No.
Confidence/level of evidence: 4D (Table 1).

Rationale: Flushing occurs in almost all subjects who take lipid-modifying doses of immediate-release (IR) niacin. It is the major reason for discontinuation of the drug, which has been described at rates as high as 25%–40%. 1–3 In the Coronary Drug Project (CDP), the prescribed dose of niacin was 1,000 mg thrice daily, but mean adherence was only 66%. 4 Flushing appears to be decreased and tolerance improved with the use of extended-release (ER) niacin, because rates of discontinuation of this formulation due to flushing have not exceeded 6% in short-term trials. 5–8

Flushing is best described as a feeling of prickly heat experienced mostly in the face or upper body but sometimes felt over the entire body surface (Table 2). It is often accompanied by visible erythema. Menopausal women can distinguish niacin-induced flushing from hot flashes, partly because niacin-induced flushing generally is not accompanied by diaphoresis. Rarely, a flush may be accompanied by hypotension.

Flushing is caused by the release of prostaglandin D 2 and possibly other eicosanoids from cells in the skin. 9 Tachyphylaxis of flushing with continued use of niacin is the rule. Regular, consistent dosing over days, weeks, and months leads to diminution of the frequency and severity of flushing, and this is accompanied by lesser increases of prostaglandin D 2 after niacin ingestion. 10 Administering aspirin or other inhibitors of cyclooxygenase 30 minutes to 1 hour before niacin intake can substantially reduce flushing. 11 An aspirin dose of 325 mg is commonly advised; an 81-mg dose may not be enough (Table 3). Recently, an inhibitor of the prostaglandin D 2 receptor 1 was found to inhibit niacin-induced flushing in mice and in early human trials; this compound is under clinical development. 12

The terms “no-flush niacin” and “flush-free niacin” are conventionally used for inositol hexanicotinate. In this compound, 6 molecules of nicotinic acid (niacin) are covalently attached to inositol by ester bonds. No published study has demonstrated that inositol hexanicotinate releases free niacin, leads to demonstrable increases...
in circulating niacin, or alters plasma lipid levels. Thus, there is no evidence that niacin in this formulation is bioavailable.

Skin rashes can occur with the use of niacin. These usually accompany flushing and are transient, but sometimes a rash will persist between doses. Patients often describe the rash as “hives,” but observation generally shows a spotty erythematous eruption that lacks the clearly demarcated “geographic” distribution of true urticaria. A Medline search on July 3, 2006, failed to reveal case reports of hives or urticaria associated with niacin or nicotinic acid. Nevertheless, the rash can be quite troubling and lead to the necessity of discontinuing the drug.

Lipid-modifying doses of niacin commonly increase dryness of the skin. As a result, skin problems associated with dyshydrosis, such as eczema, may be exacerbated. Niacin does not appear to increase the frequency or extent of other skin conditions such as psoriasis.

If Yes, Is There Any Evidence That These Changes Lead to Liver Failure, Liver Transplantation, or Death Due to Liver Toxicity?
Response: Yes.

Confidence/level of evidence: 1A (Table 1).

If Niacin Is Associated with Liver Test Abnormalities or Dysfunction, Is There Any Difference Between Immediate-Release, Sustained-Release, or Extended-Release Niacin Dosage Forms in Causing This Effect?
Response: Yes.

Confidence/level of evidence: 1A (Table 1).

Rationale: Shortly after Altschul and colleagues described cholesterol lowering by niacin in 1955, sustained-release (SR) formulations were developed in an attempt to reduce flushing. However, these were quickly found to be hepatotoxic in some patients. In 1961, 2 cases of jaundice and 6 additional instances of abnormal liver function test results were described in 40 patients treated with SR niacin. Although chemical hepatitis has been described with regular IR niacin at doses of ≥3 g/day, SR preparations exhibit increased hepatic toxicity. In clinical practice, Henkin et al found 8 cases of

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### Table 1

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<tr>
<th>Scale</th>
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<td><strong>Confidence</strong></td>
<td>Very confident</td>
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<td><strong>Type of evidence</strong></td>
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<tr>
<td>A</td>
<td>Well-designed RCTs, including RCTs conducted in patients who have reported adverse experiences</td>
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<tr>
<td>B</td>
<td>Reports to regulatory agencies judged to exceed population averages and reporting bias</td>
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<tr>
<td>C</td>
<td>Metabolic or clinical surrogate studies</td>
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<tr>
<td>D</td>
<td>Unknown, no appropriate evidence, or evidence considered subject to bias</td>
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**RCT** = randomized controlled clinical trial.

* Support for evidence for or against the contention that a potential human adverse experience is related to lipid-modifying medications.
The flush to the patient before first use. ER niacin has achieved greater patient acceptance with regard to flushing than IR niacin. The flush can be described as a prickly heat feeling usually concentrated on the head, neck, and shoulders. It usually occurs 15–30 minutes after the ingestion of IR niacin, 30–120 minutes after the ingestion of ER niacin, or at highly variable times after the ingestion of slow-release niacin. The flushing episode will usually last 5–60 minutes. ER niacin gives shorter durations of flushing than longer-acting formulations.

2. Flushing is a nonallergic phenomenon confined largely to the skin and affords no permanent harm, although it can be uncomfortable. Patients often tolerate minor skin discomfort of short duration, even when it occurs repeatedly; if they understand that it is an expected accompaniment of treatment without the serious implications of an allergic drug reaction. Diarrhea has been experienced with single doses of niacin >2,000 mg, but such doses are not recommended for clinical use.

3. Niacin therapy should be begun with low doses (eg, 125–250 mg twice daily or ER niacin 500 mg at bedtime) with gradual increases over a period of weeks to months. Flushing generally occurs when a threshold dose of niacin is given, in the range of 250–1,000 mg.

4. The frequency and intensity of flushing can be ameliorated by taking aspirin 325 mg, ibuprofen 200 mg, or another NSAID 30–60 minutes before niacin ingestion. Aspirin 81 mg may not provide sufficient inhibition of prostaglandin synthesis to inhibit flushing. In long-term use, it is best to limit aspirin or NSAID pretreatment to no more than 1–2 times/day, if multiple daily doses of niacin are used. Because flushing frequency diminishes over weeks or months, the patient may elect to take aspirin concomitantly with niacin for the sake of convenience.

5. Regular IR niacin, usually administered twice daily with breakfast and supper, is best taken in the middle of the meal rather than just before or just after the meal, to minimize flushing. Slow-release niacin preparations are dosed twice daily with meals.

6. Inositol hexanicotinate is sold as “no-flush” or “flush-free” niacin. This compound has never been shown to release free niacin, raise circulating niacin levels, or improve plasma lipid levels. It appears not to be bioavailable (hence the lack of flushing) and should not be used.

7. Flushing with ER niacin is minimized by taking it at bedtime. Moreover, taking ER niacin with a small, low-fat snack such as whole wheat crackers or skim milk also helps reduce flushing.

8. Flushing does not occur after every dose of niacin. In clinical trials, the median number of flushing episodes was 5 over the first 8 weeks after initiation of ER niacin.

9. The frequency of flushing diminishes with repeated and consistent dosing. Flushing rates begin to diminish by the fourth week of use of ER niacin.

10. Failure of flushing rates to diminish, or reappearance of flushing, may be due to inconsistent dosing. A niacin-free interval of ≥3 days will often necessitate retitration to avoid substantial flushing.

11. The niacin flush differs from a menopausal hot flash in that the former is generally not accompanied by sweating.

12. Alcohol, spicy foods, hot beverages, and hot baths or showers all can exacerbate flushing and may need to be timed sufficiently before or after niacin dosing.

13. Some specialists suggest that occasional prolonged or intense flushing might be shortened in duration by chewing an aspirin tablet to give buccal absorption of aspirin.
Table 3
Recommendations to healthcare professionals regarding the safety of niacin

1. Healthcare professionals may expect that 5%–10% of patients will not tolerate niacin in long-term use because of flushing. Some research clinics have been able to achieve considerably lower rates of discontinuation because of flushing. However, the usual prescription of any formulation of niacin without good patient education is unlikely to achieve a goal of 90% tolerability. See Table 2 for recommendations to reduce flushing.
2. Skin rashes associated with niacin therapy are generally not allergic but are likely related to dermal prostaglandin release and to dry skin. Rashes sometimes respond to moisturizing creams or to the occasional use of steroid creams. However, withdrawal or dose reduction of niacin may be necessary. Exacerbation of eczema may occur, but psoriasis and most other skin disorders do not seem to be affected by niacin administration.
3. Serious hepatic toxicity can occur with niacin therapy, but it is almost entirely associated with the use of slow-release formulations. IR (regular or crystalline) niacin or ER niacin generally should be used rather than SR niacin. Nevertheless, slow-release niacin in doses up to 1,000 mg twice daily can be used safely with liver function test monitoring (1) in exceptional cases in which only slow-release niacin is tolerated or (2) in clinics that have developed experience with a high-quality brand of slow-release niacin. If patients are taking concomitant statin therapy, then even mild liver toxicity from SR niacin might lead to decreased hepatic clearance of statins and potentially to serious myopathy. Therefore, in statin-treated patients, SR niacin doses should be limited to 1,500 mg total daily dose.
4. Hepatic transaminase levels should be monitored every 6–12 week during the first 6–12 month of treatment with niacin and periodically thereafter (eg, at 6-mo intervals). Withdrawal of niacin therapy or dosage reduction should be undertaken if persistent and substantial transaminase increases are found, especially if (1) they are 3 × the ULN, (2) they are accompanied by elevated bilirubin or prothrombin time, or (3) they are accompanied by symptoms of nausea, malaise, or fever.
5. Isolated increases of serum bilirubin remaining <3 mg/dL, without other signs of hepatic toxicity, may represent niacin interference with specific bilirubin transport and should not necessarily lead to dosage reduction or withdrawal.
6. Unexplained increases in prothrombin time with only minor transaminase increases may rarely be a niacin side effect. Nevertheless, because of the rarity of this effect and the lack of a drug interaction with warfarin, niacin can be safely used in patients anticoagulated with warfarin.
7. Niacin is useful for the treatment of the dyslipidemia of diabetes mellitus, especially low HDL cholesterol. Minor increases (4%–5% on average) in glucose levels result from niacin-induced insulin resistance, but these increases are often clinically insignificant or readily treated. Glycemic control in diabetes should be monitored following niacin initiation or dosage increase.
8. In some patients with impaired fasting glucose or impaired glucose tolerance, especially with fasting glucose levels of 110–125 mg/dL, the possibility of inducing clinical diabetes may outweigh the cardiovascular benefit of niacin therapy. It is reasonable to defer niacin therapy while attempting to improve glycemic status with lifestyle and dietary measures, or alternatively, niacin may be administered with careful monitoring as lifestyle and dietary measures are instituted.
9. In patients who have increased risk for developing type 2 diabetes (eg, patients with familial or ethnic predisposition), but who do not have impaired fasting glucose or impaired glucose tolerance, the cardiovascular protection afforded by niacin will often outweigh the presumed increase in the risk for developing diabetes. No increase in the risk for new-onset diabetes or hyperglycemia was evident in a long-term placebo-controlled clinical trial, in which 853 men took an average dose of approximately 2,000 mg regular niacin over 5 years.
10. The onset of type 2 diabetes (multiple fasting glucose levels >125 mg/dL or postprandial glucose levels >200 mg/dL) in a patient taking niacin should prompt consideration of niacin withdrawal or dosage reduction. Niacin-associated insulin resistance is reversible. In a few cases (such as in patients with very low HDL responding well to niacin or patients with progressive atherosclerotic disease), cardiovascular benefits might be judged to outweigh the role of niacin in inducing and perpetuating the diabetic state. In any case, if diabetes is persistent and requires medication or insulin after niacin withdrawal, the reintroduction of niacin should be considered. The reintroduction of niacin likely will require no, or only minor, changes in antidiabetic therapy.
11. On the basis of almost 2 decades of clinical evidence, niacin coadministration with a statin does not potentiate statin-related myopathic reactions. Isolated case reports of myopathy, including rhabdomyolysis, with niacin-statin combination therapy appeared early after the clinical introduction of lovastatin. These cases might have been related to other drug interactions (polypharmacy) or possibly to hepatic toxicity from earlier forms of niacin with subsequent decreased hepatic extraction of statins and increased peripheral blood statin levels.
12. In patients with myopathic reactions or clinically significant myalgia (enough to limit statin doses) while taking niacin-statin combination therapy, other contributors to myopathy should be considered, such as hypothyroidism, excessive alcohol ingestion, increased physical activity, infections, polymyositis, dermatomyositis, trauma, and drug abuse (cocaine, amphetamines, heroin, or PCP). Otherwise, recommendations for the evaluation of myopathic reactions in patients on statin monotherapy should be followed (eg, the National Lipid Association [NLA] recommendations described in Am J Cardiol 2006;97[suppl]:88C–94C).
13. In patients predisposed to statin-induced myopathy, such as those with chronic kidney disease, elderly patients, or those engaging in extreme physical activity, one may consider obtaining pretreatment CK levels before the addition of niacin to an established statin regimen. The level of pretreatment CK can be used to judge whether and how frequently to monitor on-treatment CK levels.
14. Blurred vision due to cystoid macular edema or other ocular effects can be a dose-related side effect caused by niacin administration, requiring niacin withdrawal and perhaps retreatment to a lower dose. This side effect is very rare when niacin doses <3,000 mg/day are used.
15. Niacin should not be used in the presence of active peptic ulcer disease, but a remote history of peptic ulcer is not a contraindication to niacin use. Gastroesophageal reflux disease is generally not affected by niacin.
16. Nausea and vomiting have occurred in association with higher doses of niacin but are very uncommon at doses up to 2,000 mg/day.
17. Palpitations and tachycardia are potential adverse experiences with niacin. In rare cases, this may relate to the increased incidence of “definite or suspected” atrial fibrillation found in a single large, randomized trial of high-dose, IR niacin, given in doses of 2–3 g/day. Theoretically, niacin may thus be relatively contraindicated in patients with paroxysmal atrial fibrillation. However, postoperative atrial fibrillation occurring after cardiothoracic surgery is not a contraindication to the subsequent clinical use of niacin. Furthermore, established atrial fibrillation is not a contraindication to niacin use, because the ventricular response rate is not affected by niacin.
18. Active gout is a relative contraindication to niacin use, because niacin (nicotinic acid) competes with uric acid for secretion by kidney tubules and raises serum uric acid levels by 5%–15%.
19. Laboratory abnormalities occurring with niacin may include small reductions in platelet count (mean 11% with ER niacin 2,000 mg) and serum phosphorus (mean 10% at the same dose). These abnormalities are not large enough to require monitoring and generally do not require dosage adjustment.

CK = creatine kinase; ER = extended-release; HDL = high-density lipoprotein; IR = immediate-release; PCP = phencyclidine; SR = sustained-release; ULN = upper limit of normal.
Does Niacin Therapy Cause Insulin Resistance and Hyperglycemia?

Response: Yes, although glucose increases are generally minor (<5%).

Confidence/level of evidence: 1A (Table 1).

Can It Worsen Glucose and Hemoglobin A1c Control in Patients with Diabetes Mellitus?

Response: Yes.

Confidence/level of evidence: 2B (Table 1).

Is Niacin Therapy Contraindicated in Individuals with Diabetes or Impaired Fasting Glucose?

Response: No.

Rationale: Mild hyperglycemia was noted as a side effect of niacin administration in the CDP. ER niacin at a dose of 2,000 mg/day was associated with a 5% increase in fasting plasma glucose. The hyperglycemia is caused by insulin resistance. Only a few studies have quantified insulin resistance in niacin-treated subjects. Some studies have suggested that the decrease in insulin sensitivity may average 20%–28% after 2 weeks of administration of IR niacin at 1,000 mg twice daily. In subjects aged >60 years, insulin sensitivity decreased by 55%–60% after niacin administration. Insulin secretory responsiveness does not decrease. In fact, insulin secretion may be increased as part of the homeostatic response to the decrease in the effectiveness of insulin action. The mechanism of peripheral insulin resistance may relate to a rebound increase in circulating fatty acids but not to increased muscle triglyceride content. A recent study found that the responses of glucose and insulin in a standard oral glucose test were indistinguishable before and after the administration of ER niacin 2 g at bedtime for 4 months. ER niacin was found to give a relatively small rebound increase in circulating free fatty acids, and this might account for the minimal change in glucose-insulin homeostasis. Alternatively, the prolonged administration of niacin (4 months rather than 2 weeks) may produce minimal increases in the flushing-related release of prostaglandins, whose influence on glucose-insulin homeostasis remains to be determined (Table 3).

The clinical impact of niacin-induced insulin resistance could be 2-fold. First, hyperglycemia itself appears to be associated with worsened cardiovascular outcomes. However, it must be recalled that the overall impact of niacin is to improve cardiovascular outcomes. The second consequence of insulin resistance might be to increase the frequency of new onset of diabetes in patients at risk, such as those with the metabolic syndrome. Although this is a theoretical possibility, the 5-year CDP did not show significant differences between niacin-treated and placebo-treated subjects in new prescriptions for insulin, new prescriptions for oral hypoglycemic drugs, or instances of dipstick-positive glycosuria.

Early reports suggested the substantial deterioration of glycemic control in patients with diabetes taking regular IR niacin. However, these studies used niacin doses as high as 4.5 g/day, which were sometimes used in the prestatin era to treat hypercholesterolemia. In a recent study, 64 patients with diabetes and peripheral arterial disease, receiving an average niacin dose of 2.55 g/day, were compared with 61 similar patients receiving placebo over a period of 48 weeks. The mean change in hemoglobin A1c (HbA1c) was 0.3% greater in the group receiving niacin (p = 0.04) and insulin use was 13% more frequent in niacin users over the course of the trial, compared with 4% more frequent with placebo (p = 0.09). Likewise, HbA1c increased by 0.3% (from 7.2% at baseline to 7.5% on treatment) in 52 patients receiving ER niacin 1,500 mg/day, compared with no change in 49 patients receiving placebo. In this study, niacin-treated patients tended to require additional hypoglycemic therapy more often than placebo-treated patients (24%–29% of those taking niacin vs 16% of those taking placebo, p = 0.32).

Therefore, doses of niacin used clinically today appear to result in only minor deterioration of glycemic control in most patients with diabetes. The favorable effects of niacin on high-density lipoprotein (HDL) cholesterol, triglycerides, lipoprotein(a), and low-density lipoprotein (LDL) particle size, along with its lesser effect in lowering LDL cholesterol, probably outweigh the small detriment in glycemic control in diabetes. This viewpoint is bolstered by a new analysis of data from the 5-year CDP. Patients were divided into groups according to baseline fasting glucose, to 1-hour plasma glucose levels, or to changes in fasting and 1-hour plasma glucose levels from baseline to year 1. Regardless of how the groups were defined, niacin treatment appeared as effective in reducing cardiovascular end points in patients with hyperglycemia as it did in patients with normoglycemia. The analysis included 70 niacin-treated patients with fasting plasma glucose ≥126 mg/dL and 182 niacin-treated patients with 1-hour glucose ≥220 mg/dL, and approximately twice as many placebo-treated patients for each category. Therefore, although the numbers of patients studied thus far are small, it appears that niacin might effectively reduce cardiovascular events in patients with diabetes and impaired glucose tolerance.
Does Niacin Monotherapy Cause Rhabdomyolysis, Myopathy, Myalgias, or Creatine Kinase Elevations?  
Response: No.

Confidence/level of evidence: 1A (Table 1).

Does the Use of Niacin, in Combination with a 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (Statin), Increase the Risk for These Problems Over What Would Be Experienced with a Statin Alone?  
Response: No.

Confidence/level of evidence: 2A (Table 1).

Is There Any Difference Among Different Niacin Formulations in Causing These Potential Effects?  
Response: Yes.

Confidence/level of evidence: 3B (Table 1).

Rationale: From the 1950s through the late 1980s (before lovastatin was introduced in 1987), neither the clinical nor the clinical trial experience with niacin was associated with an increased risk for muscle adverse experiences. Specifically, myopathy, rhabdomyolysis, and certain fatal rhabdomyolysis were not reported in the 3 prominent niacin clinical trials of the prestatin era, including those involving IR niacin monotherapy in the CDP, pentaeritrityl tetranicotinate in combination with clofibrate in the Stockholm Ischaemic Heart Disease Secondary Prevention Study, and IR niacin and colestipol in the Cholesterol-Lowering Atherosclerosis Study (CLAS).

Since the late 1990s, the interest in niacin as a lipid-altering drug has undergone a resurgence, starting with the clinical trial development of ER niacin. Again, no evidence emerged that niacin monotherapy increased muscle toxicity. In 1 ER niacin study, 223 subjects were randomized to ER niacin 1.5 g, IR niacin 1.5 g, or placebo for 8 weeks, and then the IR niacin was increased to 3.0 g for an additional 8 weeks. No differences in muscle adverse events, including creatine kinase (CK) levels, were reported between the treatment groups. In another study, 131 subjects were randomized to ER niacin to a maximum of 3,000 mg/day or placebo for 25 weeks. Again there were no increased muscle adverse experiences or elevations in CK levels.

Even in clinical trials of patients with chronic diseases such as diabetes, niacin monotherapy was not described as increasing the risk for muscle adverse experiences. For example, in the Arterial Disease Multiple Intervention Trial (ADMIT), 125 of the 468 patients with peripheral vascular disease were evaluated after being administered IR niacin up to 3,000 mg/day (or the maximum tolerated dose) for 48 weeks. No increased muscle adverse experiences were reported. Similarly, in the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT), when 148 patients with type 2 diabetes (47% of whom were receiving statin therapy) were administered ER doses of niacin 1,000–1,500 mg/day for 16 weeks, there were no increased muscle adverse effects reported, and, specifically, “no patient was reported to have the syndrome of drug-induced myopathy (myalgia and elevated creatinine kinase level of >10 times the upper limit of the reference range).”

Given the clinical trial evidence, such as that cited previously, concerns about the potential of niacin to cause muscle adverse experiences are generally not a factor when niacin is administered as monotherapy. Instead, such concerns arise specifically when niacin is used in combination with statins. Currently, the prescribing information for both statins and prescription ER niacin states that myopathy may be increased with their concomitant administration, and it is recommended that before using this combination, the potential benefits of niacin be carefully weighed against this potential risk when used with statins. The prescribing information for ER niacin also notes that rare cases of rhabdomyolysis have been associated with the concomitant administration of lipid-altering doses (≥1 g/day) of niacin when combined with statins, although at the same time, paradoxically, it is also stated that “in clinical studies with a combination tablet of Niaspan® [niacin; Kos Pharmaceuticals, Inc., Cranbury, NJ] and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with doses up to 2000 mg of Niaspan® and 40 mg of lovastatin daily for periods up to 2 years.”

So the questions are as follows: What prompted these labeling precautions and warnings? What is the clinical trial evidence that a drug interaction truly exists between niacin and statins that increases the risk for muscle adverse experiences?

Because of their remarkable efficacy, safety, and tolerability, statins have undergone the very highest level of research scrutiny. Statins have been studied in clinical trials involving hundreds of thousands of study participants and have been prescribed to millions of patients. One of the rare safety concerns that has arisen during statin development has been the finding of muscle adverse experiences. Early on, these unexpected findings brought uncertainty as to what may have caused, or what might potentially worsen, statin-related muscle adverse experiences. Even very rare, isolated case reports that suggested that niacin may increase the risk for statin-induced myopathy were taken seriously.

However, subsequent to these initial fears brought about by uncontrolled, isolated case reports, the results of controlled clinical trials are now known and have not substantiated an increased risk for muscle adverse experiences with the combined use of niacin and statins compared with what would be expected with the use of statins alone. In fact, even the isolated case reports of such potential drug interactions are
remarkable only in their relative absence in published medical research.

Strictly from a theoretical basis, there is little reason to suspect a significant drug interaction of niacin with statins. Clinically, the inhibition of the cytochrome P450 (CYP) enzyme system is thought to account for most statin drug interactions, particularly in those statins metabolized through the CYP 3A4 enzyme system. Because this enzyme system is involved in the metabolism of many other common drugs, drug interactions via this mechanism have clear clinical implications. In addition, impairment of the glucuronidation of statins from the administration of drugs such as gemfibrozil has been well described, also with clinical implications. However, niacin is not known to significantly impair either of these statin metabolic pathways. Instead, niacin is metabolized by conjugation with glycine, as well as oxidation-reduction reactions.

Thus, no major clinical trial has suggested a potential drug interaction, and there is no proposed theoretical mechanistic reason to expect a drug interaction. The statement of regulatory agencies that niacin may worsen statin-related muscle adverse experiences appears to be based only on a few case reports appearing early after the clinical introduction of statins. One might speculate that during the early experience with niacin and statins, niacin liver toxicity may have occasionally occurred, as most often has been described with the SR or slow-release niacin formulations in doses of >1,000–1,500 mg/day (as opposed to the IR or ER preparations). Theoretically, niacin-induced liver toxicity may have resulted in impaired statin metabolism or clearance and a subsequent increase in statin blood levels, with an increased risk for dose-related, statin-associated adverse experiences. However, in the absence of niacin hepatotoxicity, there is little evidence to support that, given an appropriate formulation, moderate and appropriate doses of niacin added to statins increase the risk for muscle adverse experiences compared with statin therapy alone.

The reason this safety issue is so important is because clinical trials of niacin-statin combination therapy have demonstrated complementary mechanisms of action that result in more global improvements in lipid parameters than the use of either agent alone. Furthermore, clinical trials evaluating the combination therapy of niacin with statins have shown some of the most favorable atherosclerotic coronary artery disease (CAD) outcomes. Given these benefits, clinicians and patients should not be burdened with the worries of potential niacin toxicities that may not exist.

For example, 1 of the treatment arms of the HDL-Atherosclerosis Treatment Study (HATS) CAD angiographic and outcomes trial evaluated the combined use of simvastatin (mean dose 13 mg/day) and niacin (slow-release or IR niacin, mean dose 2,400 mg/day) in 160 men and women with CAD. No significant increase in CK levels was found with simvastatin plus niacin compared with placebo.

ER niacin has also been studied in combination with statins. As previously discussed, ER monotherapy has specifically amassed considerable clinical trial data that do not support an increased risk for muscle adverse experiences with niacin monotherapy. Similarly, the safety of ER niacin in combination with statins has likewise been assessed, and studies have demonstrated no sign of increased muscle toxicity over that of statins alone. In a study of 269 patients who entered a 2-year extension of some of the earlier monotherapy trials, ER niacin 1,000–2,000 mg/day was administered, and 53 (20%) of the subjects in the extension study were also treated with statins. One subject taking simvastatin added to ER niacin developed myalgias but had normal CK levels. In the “Discussion” section, this report noted that in a review of previous studies of niacin-statin combination therapy, none of 239 study participants in previous studies had developed clinically significant myopathy.

Further evaluations of the safety and efficacy of ER niacin and statins occurred during the development of a fixed-dose combination product, ER niacin-lovastatin, which was the first combination lipid-altering drug. In a 1-year trial of 814 patients, ER niacin-lovastatin was evaluated in doses ranging from 500 mg/10 mg to 2,000 mg/40 mg per day. No confirmed cases of myopathy were observed; however, 7 episodes of CK elevations led to premature study discontinuation. Only 1 of the discontinuations in this 1-year study was due to CK levels >10 times the upper limit of normal, which may have been due to injuries from a hiking accident around the time of the abnormally elevated laboratory finding. Another subject had a CK level of >10 times the upper limit of normal that was thought to be due to strenuous exercise, and the patient continued in the study. These kinds of CK values are typical of what one would expect in a 1-year trial of ambulatory patients, especially when treated with a statin.

In a 28-week study of 237 patients administered ER niacin 2,000 mg, lovastatin 40 mg, and differing doses of ER niacin-lovastatin per day, the safety findings were again illustrative. The differences in the withdrawal between niacin-containing regimens and lovastatin monotherapy were almost entirely due to flushing, which is a known adverse experience with niacin. The withdrawals were not predominately due to myalgia, which is not a known adverse experience with niacin. Seven subjects did withdraw from the study because of myalgias: 2 were in the ER niacin 1,000 mg-lovastatin 20 mg group, none were in the ER niacin 2,000 mg-lovastatin 40 mg group, 1 was in the ER niacin monotherapy group, and 4 were in the lovastatin monotherapy group. These data suggest that if muscle adverse experiences are found with niacin and statin therapy, their frequency is not unlike that found with statins alone.

In another trial of 315 patients administered ER niacin-lovastatin (500 mg-20 mg to 2,000 mg-40 mg) versus atorvastatin (10–40 mg) and simvastatin (10–40 mg) for 16 weeks, a small and nonsignificant elevation was found in
CK values in all groups, without significant differences between groups, and without any cases of drug-induced myopathy. One subject receiving atorvastatin withdrew because of myalgias.49

From a purely medical practice standpoint, in a retrospective chart review of 66 patients treated with statins who were administered ER niacin, there was no evidence of increased muscle adverse experiences, such as myalgias.56 In a large, open-label, multispecialty study of 4,499 patients treated at 1,081 clinical sites with ER niacin 500 mg-lovastatin 20 mg for 4 weeks and then at 1,000 mg/40 mg for 8 weeks, no cases of myopathy were reported (defined as muscle symptoms with CK >10 times the upper limit of normal). Thirteen of the original 4,499 study subjects withdrew from the study because of elevated CK levels, with 2 of 6 subjects discontinuing specifically because of CK levels >10 times the upper limit of normal without symptoms. The remaining 4 subjects with CK levels >10 times the upper limit of normal usually had known associated trauma.57

Finally, ER niacin has more recently been evaluated with regard to potential additive benefits to statins in reducing carotid intima-media thickness. In this study, 167 statin-treated patients with known CAD were administered ER niacin 1,000 mg for 1 year. There were no reports of increased muscle adverse experiences.58

Thus, in summary, no clinical trial evidence exists that niacin alone, or when added to statins, increases the risk for muscle adverse experiences, at least at the doses most commonly studied, which usually are ≤2,000 mg/day. In contrast, multiple controlled clinical trials have demonstrated that niacin monotherapy does not increase the risk for muscle adverse experiences, again at least at doses ≤2,000 mg/day. Similarly, multiple clinical trials of niacin in combination with statins have shown no increase in muscle adverse experiences over statins alone. The only caveat to these clinical trial findings is in the event of niacin liver toxicity, which has most often been described with the slow-release formulation at doses >1,000–1,500 mg/day. Significant niacin-induced liver toxicity may theoretically impair statin metabolism, increase statin blood levels, and potentially increase dose-related statin toxicities,38 such as muscle adverse experiences.

### Are There Significant Safety Issues with Niacin Related to Other Organ Systems?

**Response:** Yes.

**Confidence/level of evidence:** 2C (Table 1).

**Rationale:** Blurring of vision, usually associated with high doses of regular niacin, has been described in case reports. The most serious cause is cystoid macular edema, which occurred without evidence of albumin leakage by fluorescein angiography. Niacin dosage from 11 case reports was typically ≥3,000 mg/day but as low as 1,500 mg/day. The edema generally resolved on cessation of niacin and was dose dependent.59,60

The development or exacerbation of peptic ulcer was described in older published research, usually with high doses of regular niacin.61 More recently, in a monitored, open-label trial of ER niacin in doses up to 2,000 mg/day involving a little more than 1,000 patient-years of experience, only 1 case of gastric ulcer was reported.25 Nausea and vomiting were also associated with high doses of regular niacin in older clinical experience. However, in a randomized, placebo-controlled, active-comparator trial, only 2% of patients assigned ER niacin reported dyspepsia as an adverse event, and this was significantly less frequent compared with dyspepsia in patients (15%) assigned to gemfibrozil6 (Table 3).

“Definite or suspected atrial fibrillation” was significantly more frequent in 853 men with CAD assigned to IR niacin in the CDP than in 2,115 men assigned to placebo. The fraction of men reporting this arrhythmia over 5 years was 4.7% in the niacin-treated group, compared with 2.9% in the placebo group, a 62% increase (p <0.01).4 The CDP remains the largest long-term, randomized, controlled experience with niacin to date. Nevertheless, it should be noted that atrial fibrillation has not emerged as a significant adverse event in numerous other smaller, randomized, controlled niacin trials. These later trials mostly enrolled subjects without CAD (Table 3).

Niacin in doses up to 2,000 mg/day produced increases as high as 11% in mean uric acid levels (p = 0.01), but the levels remained within normal limits.6,8 In a comparative trial, the mean increase in uric acid levels was smaller with ER niacin than with IR niacin dosed at 500 mg thrice daily (5.8% vs 16.2%, respectively, p = 0.001).7 One patient in this study developed gout after doubling the prescribed dose of ER niacin for 4 days at his own initiative, whereas 1 patient in the IR niacin group was withdrawn because of an elevated uric acid level. The mechanism of uric acid increase appears to be the competitive inhibition of the tubular secretion of uric acid by niacin (nicotinic acid)62 (Table 3).

Other laboratory variations reported with niacin therapy include small reductions in platelet count (mean 11% with ER niacin 2,000 mg) and increases in prothrombin time (mean 4%). Niacin has also been associated with small (10%) decreases in serum phosphorus.43 These changes have been regarded as clinically insignificant.

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Nicotinic acid, or niacin, has been recognized for >50 years as therapy for the vitamin B₃ deficiency disorder pellagra and as a cholesterol-lowering agent. During its long-term use in the latter capacity, its favorable effects on lipid profile and on cardiovascular risk, as well as its spectrum of side effects, have been well documented. Although niacin has shown no severe toxicities, as documented in clear and well-supported detail in the report by Guyton and Bays in this supplement, its side effects have tended to discourage widespread use. The dominant side effect is cutaneous flushing, with variable severity among patients; in addition, infrequent hepatic toxicity, hyperglycemia, gout, and rare retinal macular edema have been reported. All these effects are niacin dose dependent and fully reversible given timely discontinuation. Much of the lore on niacin stems from studies of the immediate-release (IR) and the very-slow-release preparations. Hepatic toxicity and flushing have been favorably affected by recent preparations that attempt to strike a beneficial balance between the duration and the peak levels of plasma drug exposure. During this long period of niacin observation and investigation, we have come to better understand the dosing requirements for its effective use in cardiovascular prevention. When prescribing niacin, physicians can improve outcomes if they (1) use daily doses of no more than about 2 g of prolonged-release niacin, and 4 g of IR niacin, as tolerated; (2) avoid high or prolonged plasma levels; and (3) gradually increase the daily dose over a 1- to 4-month period to reach the target dose. New prescription preparations designed around these principles compare favorably with older preparations.

**Why Bother with This Old Drug?**

The widespread perception is that the next era of cardiovascular prevention will focus on therapy for dyslipidemia, particularly on raising high-density lipoprotein (HDL) cholesterol. Given the clearly established cardiovascular benefits from statins, HDL cholesterol–raising drugs will most commonly be given in combination with low-density lipoprotein (LDL) cholesterol–lowering drugs. Thus, niacin is experiencing renewed interest because it is the most effective currently available agent for raising HDL cholesterol and increasing lipoprotein particle size, it is the only lipid drug that lowers lipoprotein(a), and it is comparable with fibrates in achieving striking reductions in triglyceride levels. Its best days may lie ahead.

As a long-term user and investigator of niacin combination therapy, I can offer the following thoughts on niacin’s resurgence. First, on the basis of strong epidemiologic evidence and published clinical trials, I have great enthusiasm for combination therapies focused on LDL cholesterol and HDL cholesterol. An important question is whether niacin will become the dominant HDL cholesterol–raising component of such therapies. This will happen only if niacin proves clinically more effective, or cost effective, than newly emerging HDL cholesterol–active agents and if its principal limiting side effect, flushing, can be reduced to a minor issue. In this regard, extended-release (ER) niacin preparations have reduced the frequency of severe or moderately severe flushing by >80% in comparison with IR crystalline niacin. Despite this important advancement, flushing remains a common complaint in the subgroup of flush-sensitive patients, a common reason for some physicians to reject niacin use out of hand, and the basis for a 6%–10% early drug discontinuation by patients. A recent development along these lines is a modified version of ER niacin that gives even lower peak niacin plasma levels and results in reduced flushing.

The overarching reason for niacin’s underuse, as described by Guyton and Bays, is the relative complexity of its initiation. Key aspects are flushing, dose up-titration over 1–4 months, aspirin coadministration, timed snacks before bedtime, and the need for more than the usual amount of counseling and patient (and physician) education. However, the effort expended to promote sustained adherence to the niacin regimen will be rewarded after 1 or 2 months, when patients develop surprising degrees of tolerance of the flushing response.

Flushing appears to be due to the subcutaneous release of prostaglandin D₂ mediated by niacin’s action as a pharmacologic ligand for the adipocyte and macrophage G protein–coupled receptor 109A, also known as HM74 in humans. Its physiologic ligand is β-hydroxybutyrate. This recent insight has led to the development and investigation of an agent (MK-0524) that blocks the G protein–coupled receptor 109A–mediated release of prostaglandin D₂ and thus flushing.

In summary, as documented in this supplement, current preparations of niacin are as safe as, or safer than, the commonly used statins or fibrates. Niacin provides comparable lipid, clinical, and angiographic benefits in patients with, or without, diabetes mellitus. There is no com-
pelling evidence of niacin-induced myopathy. Virtually all of niacin’s side effects are reversible with drug discontinuation or dose reduction. The principal side effects, cutaneous flushing and related itching and tingling, are the subject of recent drug development programs that promise to further diminish the impact of these nuisance side effects on patient compliance. As with any drug, the impact of adverse drug-related events must be weighed against therapeutic benefits. In this comparison, niacin does well. Niacin is currently the most effective therapy available for dyslipidemia, raising HDL cholesterol by 25% as monotherapy and lowering triglyceride levels by 30%–35% and lipoprotein(a) levels by 25%. As monotherapy, IR niacin at a dose of roughly 2.5 g/day reduced nonfatal myocardial infarction and stroke by 26% and 27%, respectively. In combination with moderate-dose statins, niacin reduces LDL cholesterol by 40% and increases HDL cholesterol by 30%. Epidemiologic data predict that a 40% reduction in LDL cholesterol, in combination with a 30% increase in HDL cholesterol, would reduce coronary artery disease risk by roughly 70%, , 18, 29. Indeed, in the approximately 700 patients studied in 5 published placebo-controlled, randomized clinical trials, coronary disease regressed, and major cardiovascular events were reduced by 67% relative to controls. This compares with the well-documented 25%–35% cardiovascular risk reduction with statin monotherapy.  

The National Heart, Lung, and Blood Institute’s trial AIM HIGH: Niacin Plus Statin to Prevent Vascular Events, currently in enrollment, proposes to define the magnitude of benefit of combined simvastatin plus ER niacin 2 g/day compared with simvastatin plus active placebo over a 4-year median follow-up period. This result should be available in 2010.


Safety Considerations with Omega-3 Fatty Acid Therapy

Harold E. Bays, MD

It has been suggested that the potential antithrombotic effect of fish oils may theoretically increase the risk for bleeding, which may be a safety concern for individual patients. However, clinical trial evidence has not supported increased bleeding with omega-3 fatty acid intake, even when combined with other agents that might also increase bleeding (such as aspirin and warfarin). Another potential safety concern is the susceptibility of omega-3 fatty acid preparations to undergo oxidation, which contributes to patient intolerance and potential toxicity. Finally, large amounts of fish consumption may result in adverse experiences due to the potential presence of environmental toxins such as mercury, polychlorinated biphenyls, dioxins, and other contaminants. The risks of exposure to environmental toxins and hypervitaminosis with fish consumption are substantially reduced through purification processes used to develop selected concentrated fish oil supplements and prescription preparations. Thus, in choosing which fish oil therapies to recommend, clinicians should be aware of available information to best assess their relative safety, which includes the US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) advisory statement regarding fish consumption, the meaning of certain labeling (such as “verification” through the US Pharmacopeia) and the differences in FDA regulatory requirements between nonprescription fish oil supplements and prescription fish oil preparations, and how all of this is important to the optimal treatment of patients. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:35C–43C)

Does Therapy with Fish Oils Rich in Omega-3 Fatty Acids Increase the Risk for Bleeding, and Are They Contraindicated in Patients Treated with Antiplatelet and Anticoagulant Therapies?

Response: No.

Confidence/level of evidence: 2C (Table 1).

Rationale: Because of the cardiovascular benefits of omega-3 fatty acids, the American Heart Association (AHA) has recommended omega-3 fatty acid intake in the form of routine fatty fish (as well as foods rich in α-linolenic acid) for patients without atherosclerotic coronary artery disease (CAD), fish or fish oil supplements for patients with CAD, and high-dose fish oil capsules for patients with hypertriglyceridemia. However, as with all pharmaceuticals, potential adverse experiences exist.

Fish oils rich in omega-3 fatty acids inhibit thrombosis, which has sometimes been suggested to account partially for the associated reduced risk for sudden cardiac death and reduced all-cause mortality. In vitro, fish oils competitively inhibit cyclooxygenase (and thus decrease the synthesis of thromboxane A2 from arachidonic acid in platelets), which leads to decreased platelet aggregation. Blood rheologic features and flow are also improved. Platelet-derived, growth factor–like protein is decreased, and synthesis of the platelet activation factor is decreased as well, all potentially contributing to a decrease in clinical atherothrombosis. Data regarding the effects of fish oils on fibrinogen and clotting factors are more limited. In contrast to this in vitro data, the in vivo human data are less definitive, and even the most common antithrombotic effects attributable to fish oils, such as a decrease in platelet aggregation, have not yet been definitively demonstrated in clinical trials. In fact, some human studies have demonstrated that fish oil omega-3 administration has no effect on platelet aggregation. Furthermore, low-dose fish oil therapy (<1 g/day of omega-3 fatty acids) appears to have little effect on atherothrombotic factors such as platelet-derived growth factor. Given that omega-3 fatty acid therapy has been shown to have favorable effects on cardiovascular end points with doses as low as 1 g/day, this suggests that the cardiovascular clinical benefits of fish oils are more likely related to antidyshrhythmic effects compared with antithrombotic effects.

Nonetheless, because an antithrombotic effect is possible, it has been suggested that fish oils could potentially increase the risk for bleeding. Furthermore, although the consumption of fish high in omega-3 fatty acids may decrease the risk for thrombotic stroke, it has been suggested that fish oil omega-3 therapy may actually result in a slightly higher risk for hemorrhagic stroke.
So the question is as follows: Do the potential antithrombotic effects of fish oils rich in omega-3 fatty acids pose a significant risk for increased bleeding in clinical practice, particularly when combined with other antiplatelet or anticoagulant therapies? In short, the clinical trial evidence suggests that if such an increased bleeding risk exists, the risk is very small and not of clinical significance. Clinical trials have shown high-dose fish oil omega-3 fatty acid consumption to be safe, even when concurrently administered with other agents that may increase bleeding, such as aspirin and warfarin. In fact, in certain clinical settings, it could be argued that the reported antiatherothrombotic effects of fish oils rich in omega-3 fatty acids are a benefit that outweighs the unproved bleeding risks, especially in select patients at high risk for thrombosis, which may include patients with acute atherosclerotic CAD. Finally, it is important to note that on the basis of existing clinical trial outcomes data, the AHA has recommended omega-3 fatty acid consumption (about 1 g of eicosapentaenoic acid [EPA] plus docosahexaenoic acid [DHA] per day in the form of fatty fish or fish oil supplements) in patients with documented atherosclerotic CAD, most of whom also would likely be treated with antithrombotic agents such as aspirin.

**Recommendations to healthcare professionals (Table 2):** Clinical trial data are lacking for every conceivable patient situation. From a practical standpoint, clinicians should be aware of regulatory recommendations included in the prescribing information of Omacor (Solvay Pharmaceuticals, Inc., Marietta, GA), the only prescription fish oil preparation. The drug interaction with anticoagulant section states, “Some studies with omega-3 acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor® and concomitant anticoagulants. Patients receiving treatment with both Omacor® and anticoagulants should be monitored periodically.”

Thus, a commonsense approach in treating patients routinely consuming significant amounts of fish oils, including prescription fish oils or supplements (in each case >1 g/day of EPA and DHA), would be to use similar general guidelines applicable to other anticoagulants. For example, it
postoperative management of patients undergoing major surgery.27

Fish oils should probably be discontinued during acute bleeding episodes, such as hemorrhagic stroke.28

Clinicians need to educate patients of the wide variance in fish oil therapies regarding efficacy, tolerability, and perhaps even safety. For example, the efficacy of fish oil therapy is most dependent on the amount of omega-3 fatty acids (such as EPA and DHA) in each capsule, not the total amount of fish oil concentrate. Thus, to achieve the same level of omega-3 fatty acid intake, patients may have to take as many as 11 capsules of some fish oil supplements to match the same amount of omega-3 fatty acid intake as 4 fish oil capsules of prescription fish oil.

The clinical trial evidence does not support an increased bleeding risk with fish oil therapy, even when used in combination with other agents that may increase bleeding (such as aspirin and warfarin). It is reasonable to monitor patients treated with fish oils and anticoagulants for potential bleeding adverse experiences; however, it is unclear if more monitoring is required than what would otherwise be done with patients administered anticoagulants alone. Fish oils should probably be discontinued during acute bleeding episodes, such as hemorrhagic stroke.

The decision to discontinue fish oils days before an invasive procedure at high risk for bleeding complications should be based on weighing the unproved potential increase in bleeding risk versus the potential reduction in atrial fibrillation before certain procedures, such as coronary artery bypass surgery.

Rigorous purification processes involved in fish oil manufacturing reduce the risk of fatty acid oxidation, hypervitaminosis, and exposure to environmental toxins. Clinicians and patients should be aware of the variance in the purification processes among different fish oil manufacturers. Because fish oil supplements are generally regarded as safe, they are not subject to FDA premarket and approval requirements. If a product has the “USP-Verified” mark on its label, the manufacturer has met voluntary USP standards, which include initial and ongoing determinations to ensure that (1) what is on the label is in fact in the bottle (all the listed ingredients in the declared amounts), (2) the supplement does not contain harmful levels of contaminants, (3) the supplement will break down and release ingredients in the body, and (4) the supplement has been made under current good manufacturing practices. Some fish oil manufacturers advertise voluntary compliance with the standards set by the CRN, which suggests that the fish oil manufacturers are adhering to a voluntary monograph developed by an association of manufacturers in the dietary supplement industry that specifies quality standards for fish oil supplements marketed in the United States.

Claims of a fish oil supplement being “pharmaceutical grade” have little meaning regarding safety and have even less meaning with regard to efficacy, unless the fish oil preparation has been approved by the FDA as a prescription pharmaceutical. Prescription fish oil preparations undergo the same rigorous FDA regulatory requirements as other prescription pharmaceuticals, with regard to both efficacy and safety. One of the most common pitfalls in the day-to-day, clinical use of fish oil therapy is the sense among patients that all fish oil therapies are the same. Clinicians need to educate patients of the wide variance in fish oil therapies regarding efficacy, tolerability, and perhaps even safety. For example, the efficacy of fish oil therapy is most dependent on the amount of omega-3 fatty acids (such as EPA and DHA) in each capsule, not the total amount of fish oil concentrate.

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CRN = Council for Responsible Nutrition; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FDA = US Food and Drug Administration; USP = United States Pharmacopeia.
and particularly the potential toxicities of fish oil therapy involve the manner in which the fish oil products are manufactured, specifically regarding purification processes directed at the removal of toxins, non–ω-3 fatty acids, oxidized substances, and other undesirable byproducts.\textsuperscript{25} In fact, it could be argued that when a patient describes a fish oil supplement as having a strong, rancid fishy smell and taste, this may suggest that the supplement was poorly purified by the manufacturer or has expired or become oxidized and is potentially toxic.

**Hypervitaminosis:** Hypervitaminosis is another potential toxicity that may occur with the excessive consumption of fish oils containing high concentrations of fat-soluble vitamins D and A, as might occur with excessive cod liver oil consumption. Very high vitamin D intake can cause hypercalcemia,\textsuperscript{32} but this has not been a widely described consequence of any fish oil consumption, including cod liver oil ingestion. Similarly, studies suggest that vitamin A toxicity is rare when fish oils are administered in oil-based preparations.\textsuperscript{33} Nonetheless, the excessive intake of vitamin A (particularly in water-miscible, emulsified, and solid forms) has been described to cause yellowish discoloration of the skin (carotenemia); possibly an increased risk for lung cancer\textsuperscript{34}; teratogenic effects in pregnant women\textsuperscript{35}; severe anemia and thrombocytopenia in infants\textsuperscript{36}; toxicities to the musculoskeletal, neurologic, and gastrointestinal system in children\textsuperscript{37}; bone pain; and osteoporosis, with an increased risk for bone fractures in older subjects.\textsuperscript{38}

In the early 1900s, rickets (a bone disease due to vitamin D deficiency) was rampant among poor children in the United States and England who were living in industrialized cities amid polluted, smoky skies. Vitamin D deficiency ensued because sunlight is needed to metabolize vitamin D. Around this same time, cod liver oil (an omega-3 fatty acid) was found to be useful to prevent rickets because it contained substantial amounts of vitamin D.\textsuperscript{39} Cod liver oil also was used as a supplement to treat a variety of many pediatric ailments, partly because it also contained high doses of vitamin A, and vitamin A deficiency was thought to contribute to blindness and immune deficiencies and thus an increased risk for infections. Thus, it was not uncommon for parents to administer cod liver oil routinely to their children and for pediatricians to recommend infant formulas that included cod liver oil.

However, since the fortification of infant milk preparations with vitamins D and A in the 1930s, the use of cod liver oil to prevent rickets is no longer common in the United States.\textsuperscript{39} US pediatricians no longer routinely recommend cod liver oil for infants, although cod liver oil remains a component of some “homemade” infant formulas. Thus, clinicians should be made aware that cod liver oil supplementation is still common in some populations, such as those in northern Europe, and thus may represent at least a potential risk for hypervitaminosis.

**Environmental toxins:** High fish oil intake through the consumption of large amounts of fish may present a risk for increased environmental toxin exposure.\textsuperscript{40–42} For example, excessive mercury exposure may originate from industrial sources (such as coal-fired power plants, waste incinerators, and certain factories and mining operations). Once airborne, the mercury pollutants fall to the ground in rain or snow, become deposited in water bodies, and are subsequently converted by bacteria into methylmercury, which is highly toxic to humans.\textsuperscript{43} Larger and older fish may have more time to bioaccumulate mercury from their food (and through their gills) than smaller and younger fish.\textsuperscript{44} Furthermore, large predatory fish near the top of marine food chains may accumulate more mercury than fish lower in the marine food chain through the consumption of small fish, resulting in biomagnification. Mercury poisoning through fish consumption has resulted in various neuropsychiatric signs and symptoms, including constriction of the bilateral visual fields, paraesthesia of the extremities and mouth, ataxia, incoordination, tremor dystathria and auditory impairments, severe neurologic damage to children born to mothers with toxic mercury exposure,\textsuperscript{43,45} and other signs and symptoms.\textsuperscript{46} As a testament that mercury exposure poses real risks to populations, in 2004, the US Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) issued an advisory statement recommending that women who may become pregnant, women who are pregnant, breast-feeding mothers, and young children avoid eating some types of fish and eat fish and shellfish that are lower in mercury.\textsuperscript{47} However, the totality of evidence supports that the benefits of fish intake generally exceeds the potential risks, including intake in women of childbearing age, except for a few selected fish species.\textsuperscript{48} It is noteworthy that these recommendations apply only to fish oil intake through the consumption of fish. With regard to fish oil intake through select fish oil supplements, testing has shown that the level of mercury (and other environmental toxins) is very low or negligible.\textsuperscript{49,50} This is probably due to 2 factors. First, the oxidized mercury released from power plants and potentially washed into local water bodies by rainfall is water soluble.\textsuperscript{51} Thus, although mercury toxicity may sometimes be a potential issue with the consumption of the flesh of fish, oxidized mercury is insoluble in oil and thus would not be expected to represent a significant toxicity risk with the intake of the oils of fish. Second, selected fish oil supplements undergo extensive purification processes to remove environmental and other toxins, with prescription fish oil preparations undergoing even more rigorous regulatory processes to achieve FDA approval as prescription pharmaceuticals.

Before 1980, polychlorinated biphenyls (PCBs), colorless and odorless chemicals, were used widely in flame retardants, pesticides, paints, varnishes, inks, lubricants, and insulation related to electrical equipment, such as transformers. Since then, PCBs have been banned by most countries.\textsuperscript{43} As with mercury, PCBs are toxic to humans as well
as to fetuses.\textsuperscript{43,52} PCBs are a probable human carcinogen. Acute PCB toxicity most commonly manifests as chloracne lesions or rashes. Other manifestations of PCB toxicity include elevated liver enzymes and possibly an increased risk for goiter. Finally, exposure to PCBs in utero may result in genetic alterations or mutations in a fetus’s reproductive organs (feminized unborne males, intersexed fetuses, or the in utero development of male and female reproductive organs), and in utero or breast milk exposure to newborns may result in neurodevelopmental delays, impaired cognition, and immune deficiencies.\textsuperscript{43}

Other environmental toxins include organochlorine (OC) pesticides, which were sprayed on crops and forests and released into the air, water, and soil. One of the best known OCs is dichlorodiphenyltrichloroethane (DDT), which has been banned in the United States since the 1970s. DDT is highly toxic to fish, and its widespread use was a major reason for the near extinction of the bald eagle in the 1950s. Although the clinical manifestations of OC toxicity may not be as clear as other toxins, OCs may cause abnormalities in liver enzymes and chloracne\textsuperscript{53} and contribute to neurologic impairment, such as Alzheimer disease.\textsuperscript{54}

Dioxins, which are another family of chemical compounds called polychlorodibenzo-oxinoids (sometimes grouped as part of OCs), are a byproduct of industrial processes involving chlorine, such as waste incineration, chemical and pesticide manufacturing, and pulp and paper bleaching. Dioxin was the primary toxic component of Agent Orange, a defoliant used during the Vietnam War, and is considered a likely carcinogen. Dioxin toxicity is commonly manifested by chloracne and has also been suggested to contribute to the onset of diabetes mellitus, endometriosis with infertility, abnormalities in thyroid function, and impaired neurodevelopment of infants.\textsuperscript{55}

Just as with mercury, fish consumption has sometimes been associated with toxicities from all of these environmental toxins.\textsuperscript{40–43,55,56} Thus, manufacturers of selected fish oil supplements have implemented various purification processes and quality controls designed to reduce the risk for exposure to environmental toxins. Largely through these quality measures, reviews of 5 commercial fish oil supplement have concluded that some of the more common fish oil supplements contain fewer toxins than fish and that fish oil supplements may be preferable to fish consumption as a therapeutic source of omega-3 fatty acids.\textsuperscript{50,56}

Recently, a prescription omega-3 fatty acid fish oil preparation has been approved for the treatment of hypertriglyceridemia (Omacor). In multiple clinical trials of this prescription omega-3 fatty acid agent,\textsuperscript{25} no cases of hypervitaminosis or illnesses due to exposure to environmental toxins were reported. This safety profile is likely owing to an extensive purification process resulting in no detectable concentrations of heavy metals, halogenated polycarbons, and dioxins, as well as <0.05% of trans-fatty acids.\textsuperscript{25}

**Recommendations to healthcare professionals (Table 2):** In choosing the most appropriate fish oil therapy to recommend to patients, clinicians should be aware of potential fish oil toxicities and know which fish oil manufacturers have adequate purification processes to minimize these potential toxicities. This can present a challenge, because although the FDA has regulatory mechanisms to ensure the safety of prescription products,\textsuperscript{57} no such FDA regulatory mechanisms are in place for “dietary supplements.” Agents classified as dietary supplements do not require product registration, manufacturer registration, pre-market approval, or the mandatory reporting of adverse events and require only limited safety-related labeling. From a practical standpoint, this means that manufacturers of dietary supplements are not required to provide evidence of efficacy, safety, or manufacturing standards before marketing products.\textsuperscript{58} Although it has been suggested that this lack of oversight and inadequate regulation may pose a risk to the health and safety of the public,\textsuperscript{58} and although organizations such as the American Medical Association (AMA) have advocated that dietary supplements be regulated to the same standards as prescription and over-the-counter drugs,\textsuperscript{59} in the current regulatory environment, clinicians should be aware of the quality assurance practice guidelines for fish oil products, self-established by their manufacturers, before recommending any dietary supplement.

For example, specific FDA current good manufacturing practices are required for the prescription pharmaceuticals and describe procedural protocols that help ensure acceptable quality.\textsuperscript{60} Current good manufacturing practices are currently under development for dietary supplements (Table 3). In the interim, fish oil supplements are included on the list of substances that the FDA designates as “generally regarded as safe,” which means that according to qualified experts, fish oils have adequately been shown to be safe under the conditions of their intended use. As with other products generally regarded as safe, fish oils supplements are not subject to the prem Market review and approval requirements of the FDA. Nonetheless, some fish oil manufacturers include in their advertisements that fish oil supplements have been designated by the FDA as generally regarded as safe and that their manufacturing processes are in voluntary compliance with current good manufacturing practices. With regard to efficacy (and safety) in the clinical use of fish oil supplements, the FDA has determined that the following statement is acceptable, provided that fish oil supplement manufacturers do not recommend or suggest in their labeling a daily intake that exceeds 2 g/day of EPA and DHA: “Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease. The FDA evaluated the data and determined that, although there is scientific evidence supporting the claim, the evidence is not conclusive.”\textsuperscript{61}

Because of the recognition that “faith” alone is not sufficiently reassuring to many clinicians or patients regarding medicinal product quality and safety, some fish oil supplement manufacturers elect to pursue “USP-Verified” marks
A USP-Verified mark indicates compliance with standards set by the United States Pharmacopeia (USP), an independent, not-for-profit organization established in 1820 that has quality standards enforceable by the FDA and sets the legally recognized standards for identity, strength, quality, purity, packaging, and labeling. Many clinicians are aware of USP monographs, mostly issued for prescription or over-the-counter products and sometimes for dietary supplements as well. A USP monograph is a descriptive document that typically contains the following information about a product: descriptive information (graphic formula, chemical formula, molecular weight, chemical name, and chemical abstracts registry number), percentage of the active ingredient in the product, a discussion of product packaging and storage, USP reference standards, any official revisions to the monograph, tests used to identify the product, melting temperature range, amount of water, residue on ignition, and a list of tests and procedures to assess toxins and impurities. No official USP monograph currently exists for nonprescription fish oil supplements.

Beyond describing monograph specifications of products, the USP is also engaged with the verification of products, such as through the voluntary Dietary Supplement Verification Program. The presence of the distinctive USP-Verified mark on its label signifies that the USP has rigorously tested and verified a supplement to ensure that (1) what is on the label is in fact in the bottle (all the listed ingredients in the declared amounts), (2) the supplement does not contain harmful levels of contaminants, (3) the supplement will break down and release ingredients in the body, and (4) the supplement has been made under current good manufacturing practices. If a product has a USP-Verified mark on its label, the manufacturer is legally responsible for meeting USP standards. Two separate USP verifications exist. One distinctive USP-Verified mark is “Ingredient Verified.” In this case, the USP has performed testing at the request of the manufacturer to verify the consistent quality of active and inactive ingredients. This mark is used mainly by manufacturers. The other distinctive USP-Verified mark is “Dietary Supplement Verified,” indicating that testing has been done to ensure the integrity, purity, dissolution, and safe manufacturing of a dietary supplement. This mark is for mainly for consumers. At the time of this writing, only a few fish oil supplement manufacturers have voluntarily requested and subsequently received either of these USP-Verified designations.

To assist in the establishment of quality and safety standards that might form the basis of an official USP monograph for the class of nonprescription fish oil supplements, the Council for Responsible Nutrition (CRN) developed a voluntary monograph aimed at the goal of “raising the bar” through quality standards for fish oil supplements marketed in the United States. The CRN is an association of ingredient suppliers and manufacturers in the dietary supplement industry founded in 1973 for the purpose of “improving the environment for member companies to responsibly market...
dietary supplements by enhancing confidence among media, healthcare professionals, decision makers and consumers" and has encouraged the incorporation of this voluntary monograph into existing standards established by organizations such as the USP, as well as other organizations such as the American Oil Chemists Society and the Association of Official Analytical Chemists International. Some fish oil manufacturers claim voluntary compliance with the proposed CRN fish oil monograph.

Currently, the USP is providing its verification mark on the basis of a proposed monograph, which was derived from the CRN monograph, as well as other resources. The establishment of an official USP monograph for fish oil therapy is imminent. However, even with the establishment of an official USP monograph, clinicians and patients should understand that no USP designation exists to qualify omega-3 fish oil supplements as “pharmaceutical grade,” as claimed by some fish oil manufacturers in their advertisements. The USP has no standards that defined the term “pharmaceutical grade”; thus, any labeling of an omega-3 fish oil supplement as “pharmaceutical grade” as it pertains to the USP is misleading. In fact, it might better be considered as blatantly inaccurate, unless the fish oil formulation has gone through the rigorous processes and oversight required to receive approval as a prescription pharmaceutical from an established regulatory agency such as the FDA (Table 1).

So the answer as to whether prescription and/or supplement omega-3 fatty acid products may contain excessive vitamins or environmental toxins in sufficient concentrations to pose a potential health risk is dependent almost entirely on the purification process. With nonprescription fish oil supplements, because no FDA regulatory oversight exists to ensure a lack of included toxins, clinicians and patients must rely on their faith in the voluntary commitment to quality on the part of manufacturers or ensure that the fish oil supplement manufacturers have complied with accepted quality assurance standards, as denoted by labeling such as “USP-Verified.” The only caveat here is that any such labeling does not verify, or even address, the degree of efficacy of a supplement. For efficacy information, a label must be read to assess the amount of EPA and DHA within a fish oil dietary supplement, which can then be used to determine the anticipated therapeutic response. This is important because although the front of the bottles of some fish oil supplements may list the contents as having “1,000 mg of fish oil concentrate,” the labeling on the back of the bottles may reveal that the amounts of the actual omega-3 fatty acids (eg, EPA and DHA) are much less, often as low as 300 mg per fish oil capsule. In this case, from a practical standpoint, a patient would have to consume 11 fish oil capsules containing 300 mg EPA and DHA to achieve the same omega-3 fatty acid intake as 4 tablets of prescription fish oil (which contains 840 mg of EPA and DHA).

If a fish oil preparation has received FDA approval as a prescription pharmaceutical, clinicians and patients can be assured that the manufacturer has met rigorous FDA regulatory requirements with regard to both efficacy and safety when used in the clinical setting and at the doses in compliance with the prescribing information.

17. O’Keefe JH Jr, Abuissa H, Sastre A, Steinhaus DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial


Expert Opinion: Omega-3 Fatty Acids and Bleeding—Cause for Concern?

William S. Harris, PhD

Omega-3 fatty acid ethyl esters have well-known triglyceride-lowering properties and were shown >30 years ago to inhibit platelet function. With the recent US Food and Drug Administration (FDA) approval of these agents for treating severe triglyceride elevations, concerns about excess bleeding naturally arise. However, an objective assessment of the evidence for clinically significant bleeding reveals that such concerns are unfounded. As such, the benefits of triglyceride lowering with omega-3 fatty acids more than outweigh any theoretical risks for increased bleeding. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:44C–46C)

As the health benefits of omega-3 fatty acids become clearer, interest in defining the potential adverse effects of these nutrients naturally increases. In the review by Bays1 in this supplement, the possibility of increased risk for bleeding with omega-3 fatty acids is addressed. Bays clearly describes the role of omega-3 fatty acids in eicosanoid metabolism, which forms the biochemical basis for the concern for increased bleeding with omega-3 fatty acids. He concludes that although there is little evidence for increased risk for clinically significant bleeding with omega-3 fatty acid supplementation, clinicians should be mindful of this as a theoretical possibility. This commentary provides a more detailed discussion of the evidence supporting this conclusion.

The relevant clinical question is the following: What is the evidence that taking long-chain omega-3 fatty acids in doses of 1–4 g/day causes clinically significant bleeding? To answer that question, studies were examined in which these doses (and typically even greater doses) were provided to patients who underwent major vascular surgery (coronary artery bypass grafting or endarterectomy) or femoral artery puncture for either diagnostic cardiac catheterization or percutaneous transluminal coronary angioplasty.

There have been 2 studies in which patients who underwent coronary artery bypass grafting were given omega-3 fatty acids, 2 trials including carotid endarterectomy, and 15 trials in which omega-3 fatty acids were tested in patients who underwent femoral artery catheterization. These studies are summarized in Table 1,2–20 along with the concomitant medications and findings with regard to bleeding complications. In these studies, the risk for clinically significant bleeding was virtually nonexistent.

Several years ago, Knapp21 reviewed the published research regarding omega-3 fatty acids and human thrombosis and hemostasis. In addition to noting the lack of significant bleeding with omega-3 fatty acid supplementation in cardiovascular studies to date, he also referred to studies in pregnant women in which supplementation with omega-3 fatty acids 2.7 g/day did not lead to increased blood loss at delivery,22 and he noted that supplemented dialysis patients were not at increased risk for bleeding.23,24 There had been 1 report that fish oil (5 g) caused increased risk for nosebleeds in children with hypercholesterolemia,25 but this could not be replicated in a later trial in children on dialysis.26

Thus, the experience has been virtually unanimous: omega-3 fatty acid supplements do not increase the risk for clinically significant bleeding, even in patients also being treated with antiplatelet or antithrombotic medications. Anecdotal reports of an increased bruising tendency have not been tested in a controlled setting, nor has the possible adverse interaction between omega-3 fatty acids and newer antiplatelet drugs (eg, clopidogrel) been examined directly.

Given our present knowledge, I would agree with Bays1 that we are “confident” that omega-3 fatty acids do not increase risk for adverse bleeding episodes. However, I would consider the evidence to be at the “A” (well designed randomized controlled clinical trials)–instead of “C” (reports to regulatory agencies; multiple case studies; strong trends; prospective cohort studies; metabolic or clinical surrogate studies)—level, given the number of randomized, controlled clinical trials in which these agents were found to be safe, bearing in mind that more studies are still needed to determine the combined effects of glycoprotein IIb/IIIa inhibitors and omega-3 fatty acids. Nevertheless, in considering the risks and benefits of omega-3 fatty acids for cardiovascular risk reduction, the latter continue to outweigh the former.

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E-mail address: bill.harris@usd.edu.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>EPA Δ DHA Δ (Product)</th>
<th>Pretreatment (days)</th>
<th>Duration (mo)</th>
<th>Patients (n)</th>
<th>Concomitant Medications</th>
<th>Bleeding Complications</th>
</tr>
</thead>
</table>
| CABG2     | 3.4 g (Omacor)        | 2                  | 12           | 610         | Aspirin or warfarin     | "The bleeding time increased moderately in both groups, and there was no group difference; only adverse events reported were: nausea (n = 4) and diarrhea (n = 1). All bleeding times were within the normal range."
| CABG3     | 3.6 g (MaxEPA)        | 0                  | 12           | 108         | None                   | "No patient had unanticipated bleeding at or after surgery compared to matched controls."
| PTCA4     | 3.6 g (MaxEPA)        | 6                  | 12           | 447         | Aspirin, dipyridamole, CCB, nitrates | "No difference in clinically significant bleeding was noted..."
| PTCA5     | 3.0 g (MaxEPA)        | 1–2               | 6            | 120         | Aspirin, dipyradimole, CCB, nitrates | "All bleeding times were within the normal range."
| PTCA6     | 5.4 g (Pomergran)     | 0                  | 4.5          | 204         | Aspirin, dipyridamole   | "No obvious adverse effects to the capsules were noted."
| PTCA7     | 5.4 g (Promega)       | 0                  | 4.5          | 194         | Aspirin                | "No obvious adverse effects to the capsules were noted."
| PTCA10    | 3.0 g (MaxEPA)        | 4                  | 2.5          | 205         | Aspirin                | "No obvious adverse effects to the capsules were noted."
| PTCA11    | 6.9 g (NIH Fish Oil)  | 0                  | 4.5          | 194         | Aspirin                | "No obvious adverse effects to the capsules were noted."
| PTCA12    | 4.5 g (Promega)       | 0                  | 4.5          | 194         | Aspirin                | "No obvious adverse effects to the capsules were noted."
| PTCA15    | 6.9 g (NIH Fish Oil)  | 0                  | 4.5          | 194         | Aspirin                | "No obvious adverse effects to the capsules were noted."
| PTCA16    | 5.1 g (Omacor)        | 0                  | 4.5          | 194         | Aspirin                | "No obvious adverse effects to the capsules were noted."
| Endarterectomy17 | 1.4 g/day (MaxEPA)  | Median 30          | Through surgery | 297 | Aspirin (100% of patients) | "No obvious adverse effects to the capsules were noted."
| PTCA19    | 4.5 g (Promega)       | 0                  | 4.5          | 194         | Aspirin                | "No obvious adverse effects to the capsules were noted."

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; CCB = calcium channel blocker; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; NIH = National Institutes of Health; Placebo: effects of omega-3 fatty acids on bleeding complications. The bleeding time increased moderately in both groups, and there was no group difference; only adverse events reported were: nausea (n = 4) and diarrhea (n = 1). All bleeding times were within the normal range. There were no clinically significant bleeding complications associated with the second episode of coronary angioplasty. This was not an issue for the cardiologists doing the caths. (F. Sacks, personal communication)


Safety Considerations with Gastrointestinally Active Lipid-Lowering Drugs

Terry A. Jacobson, MD, a,* Annemarie Armani, MD, b James M. McKenney, PharmD, c and John R. Guyton, MD d

Gastrointestinally active agents such as cholesterol absorption inhibitors (CAIs) (eg, ezetimibe) and bile acid sequestrants (BAS) (the resins cholestyramine and colestipol, or colesevelam, a nonabsorbable polymer) offer important options for lipid-lowering therapy. Ezetimibe is a novel CAI that inhibits the absorption of dietary and biliary cholesterol without affecting the absorption of triglycerides or fat-soluble vitamins. In clinical trials, there has been no evidence of increased rates of myopathy or rhabdomyolysis associated with ezetimibe, whether in use as monotherapy or in a combination with statin therapy, although there exist case reports of possible ezetimibe-associated myopathy. Ezetimibe alone does not appear to increase liver transaminase levels significantly, but the coadministration of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) with ezetimibe marginally increases this risk. However, reported increases in liver enzymes have not been associated with clinically meaningful symptoms and often return to baseline levels after the discontinuation of therapy or with continued treatment. To date, no cases of liver failure, liver transplantation, or death have been reported. BAS have been used clinically since the 1960s for lowering low-density lipoprotein cholesterol. Because they are not absorbed from the gastrointestinal tract into the blood, these agents do not contact most body organs and are therefore systemically safe. However, case reports and pharmacokinetic data disclose 3 kinds of adverse effects: (1) the decreased absorption of concomitant medications and sometimes of certain vitamins; (2) the physicochemical alteration of intestinal contents leading to constipation and, very rarely, intestinal obstruction; and (3) modest increases in plasma triglyceride levels due to the alteration of hepatic lipid metabolism. The newest BAS, colesevelam, has greater specificity for bile acids compared with the older agents cholestyramine and colestipol, eliminating most drug interactions and reducing the tendency for constipation. Overall, CAIs and BAS have excellent systemic safety profiles when used alone or in combination with other lipid-lowering drugs. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:47C–55C)

Do Cholesterol Absorption Inhibitors Cause Myopathy?

Response: No.

Confidence/level of evidence: 2B (Table 1).

Rationale: In randomized clinical trials, no evidence of increased rates of myopathy (defined as creatine kinase [CK] >10 times the upper limit of normal [ULN] with associated muscle symptoms) or rhabdomyolysis associated with ezetimibe therapy has been reported. 1,2 Additionally, no changes in CK levels have been shown with ezetimibe compared with placebo (Table 2). 1–16 Furthermore, the reported rate of muscle-related side effects with ezetimibe in combination with 3-hydroxyl-methylglutaryl coenzyme A reductase inhibitor (statin) therapy is about the same as with statin monotherapy (Table 2). 1–16 The incidence of CK ≥10 times ULN with ezetimibe alone is low (0.2%) and not different from that with placebo (0.1%). 7 When combined with a statin, the rate of CK ≥10 times ULN also has been found to be low and no different from the rate with the statin alone. For example, in a recent pooled safety analysis of 2,382 subjects, an increase in CK ≥10 times ULN occurred in 0.1% of patients receiving ezetimibe with statins (atorvastatin, simvastatin, pravastatin, or lovastatin at all doses) compared with 0.4% for statins alone. 14 In a more extensive pooled safety analysis involving 17 randomized clinical trials and 4,558 patients, the incidence of CK ≥10 times ULN was 0% with ezetimibe alone compared with 0.7% with placebo and 0.2% with an ezetimibe-simvastatin combination compared with 0.3% with simvastatin alone. 17

A recent discussion and statement on muscle and statin safety put forth by the National Lipid Association (NLA) Statin Safety Task Force has recently been published. 18 In that...
ezetimibe to statin therapy (1 with atorvastatin 80 mg/day and another with fluvastatin 80 mg/day), suggesting that ezetimibe may interact with statins to trigger statin-associated myopathy. However, neither of the 2 cases presented met the standard definition of myopathy, and both involved only small increases in CK levels, from 1.9–2.8 times ULN. One of the cases was in an asymptomatic subject, and the other occurred in a patient taking the maximum dose of atorvastatin (80 mg). Neither patient was rechallenged with ezetimibe, making the conclusions less robust. CK elevations are frequently found in patients with or without administration of lipid-altering therapies.

Furthermore, there have been other case reports associated with ezetimibe monotherapy.\textsuperscript{20–23} Most of them, however, did not involve the critical ingredients of rechallenge or consistency in measuring muscle symptoms or elevations in CK levels. For example, Phillips\textsuperscript{20} evaluated >300 patients with so-called lipido-lowering intolerance and started 30 patients with elevated fasting respiratory exchange ratios on ezetimibe monotherapy. Of these 30 patients, myopathic symptoms were reported to recur in 18 (60\%) <2 weeks after initiating therapy. Formal testing, however, was not performed, and CK levels, unfortunately, were not reported. Phillips\textsuperscript{20} suggested that an abnormal fasting respiratory exchange ratio is a proxy measure for abnormalities in fatty acid oxidation and can perhaps identify those at risk for myopathy.

Ezetimibe was described as worsening myopathy in a case report of a patient with McArdle disease.\textsuperscript{22} McArdle disease is the most common inherited glycogen disease affecting skeletal muscle, caused by mutations in the gene that encodes myophosphorylase,\textsuperscript{24} and it increases the risk for rhabdomyolysis. In this single report, 4 weeks after ezetimibe 10 mg/day was initiated, CK levels started to increase dramatically (from 837 U/L to baseline at 21,370 U/L at 24 weeks), and the patient eventually reported slight myoglobinuria and severe weakness. When ezetimibe was discontinued, CK levels returned to previous values after 4 weeks, and the patient recovered uneventfully. Unfortunately, the patient was not rechallenged, and a direct cause-and-effect relation could not be determined. Hence, it appears from the published research that only a few case reports show any type of relation of ezetimibe with myopathy and that if there is an association, it is a weak one at best.

If myotoxicity is caused by ezetimibe, the underlying pathology would need to be further elucidated. The most common plausible explanations are a cholesterol deficiency with secondary abnormal membrane behaviors, a coenzyme Q10 deficiency causing abnormal mitochondrial respiratory function, or prenylated protein abnormalities causing imbalances in intracellular protein messaging. The significance of this with regard to ezetimibe is even less clear. In combination therapy with ezetimibe and statins, a pharmacokinetic interaction might be glucuronidation.\textsuperscript{25,26} Although lipophilic statins are hydrolyzed by the cytochrome P450 enzymes to increase water solubility for renal excretion, statins are also metabolized by glucuronidation. Ezetimibe also undergoes glucuronidation, and ezetimibe and statins

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>• Well-designed RCTs, including RCTs conducted in patients who have reported adverse experiences</td>
</tr>
<tr>
<td>B</td>
<td>• Single RCT with a highly statistically significant result</td>
</tr>
<tr>
<td></td>
<td>• Well-conducted retrospective case-control studies with adverse experiences as primary endpoints</td>
</tr>
<tr>
<td></td>
<td>• Managed care claims database analysis with a highly statistically significant result</td>
</tr>
<tr>
<td>C</td>
<td>• Reports to regulatory agencies judged to exceed population averages and reporting bias</td>
</tr>
<tr>
<td></td>
<td>• Multiple case studies with nonblinded dechallenge and rechallenge</td>
</tr>
<tr>
<td></td>
<td>• Strong trends, not reaching statistical significance, for safety issues in large RCTs</td>
</tr>
<tr>
<td></td>
<td>• Well-conducted prospective cohort study, giving a result that is statistically well above population average</td>
</tr>
<tr>
<td></td>
<td>• Metabolic or clinical surrogate studies</td>
</tr>
<tr>
<td>D</td>
<td>• Undocumented opinion of experienced research investigators and clinicians</td>
</tr>
<tr>
<td></td>
<td>• Poorly controlled or uncontrolled studies</td>
</tr>
<tr>
<td></td>
<td>• Nondefinitive evidence from regulatory agency reporting systems or managed care claims databases</td>
</tr>
<tr>
<td>U</td>
<td>• Unknown, no appropriate evidence, or evidence considered subject to bias</td>
</tr>
</tbody>
</table>

\(RCT =\) randomized controlled clinical trial.\textsuperscript{a} Support for evidence for or against the contention that a potential human adverse experience is related to lipid-modifying medications.
<table>
<thead>
<tr>
<th>Trial Description</th>
<th>Duration</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Reported Muscle Symptoms</th>
<th>Placebo</th>
<th>Ezetimibe</th>
<th>Statin</th>
<th>Ezetimibe/Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe monotherapy</td>
<td>12 wk</td>
<td>892</td>
<td>Ezetimibe 10 mg</td>
<td>CK ≥10 × ULN*</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dujovne et al1</td>
<td></td>
<td></td>
<td></td>
<td>Musculoskeletal pain*</td>
<td>4%</td>
<td>5%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK ≥10 × ULN*</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK ≥3 × ULN#</td>
<td>1.5%</td>
<td>2.6%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Musculoskeletal pain*</td>
<td>4%</td>
<td>5%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK ≥10 × ULN with muscle symptoms†</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK ≥5 × ULN#</td>
<td>0%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ezetimibe-lovastatin: Kerzner et al8</td>
<td>12 wk</td>
<td>548</td>
<td>Lovastatin 10, 20, 40 mg–ezetimibe 10 mg</td>
<td>No CK ≥10 × ULN without muscle symptoms‡</td>
<td>—</td>
<td>—</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe-pravastatin: Melani et al9</td>
<td>12 wk</td>
<td>538</td>
<td>Pravastatin 10, 20, 40 mg–ezetimibe 10 mg</td>
<td>CK ≥10 × ULN with muscle symptoms§</td>
<td>—</td>
<td>—</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK ≥5 × ULN#</td>
<td>0%</td>
<td>0%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Davidson et al10</td>
<td>12 wk</td>
<td>668</td>
<td>Simvastatin 10, 20, 40, 80 mg–ezetimibe 10 mg</td>
<td>CK ≥10 × ULN with muscle symptoms¶</td>
<td>—</td>
<td>—</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Feldman et al3</td>
<td>23 wk</td>
<td>710</td>
<td>Simvastatin 10, 20, 40 mg–ezetimibe 10 mg</td>
<td>CK ≥10 × ULN with muscle symptoms**</td>
<td>—</td>
<td>—</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Goldberg et al11</td>
<td>12 wk</td>
<td>887</td>
<td>Simvastatin 10, 20, 30, 80 mg–ezetimibe 10 mg</td>
<td>CK ≥10 × ULN with muscle symptoms††</td>
<td>—</td>
<td>—</td>
<td>0.4% (10 mg-10 mg); 0.6% (10 mg-20 mg); 1.0% (10 mg-40 mg)</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Bays et al12 (UK-HARP-II)</td>
<td>6 mo (patients with CKD)</td>
<td>203</td>
<td>Simvastatin 20 mg–ezetimibe 10 mg</td>
<td>CK ≥5–10 × ULN</td>
<td>—</td>
<td>—</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>CK &gt; 10 × ULN</td>
<td>—</td>
<td>—</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe added to statin: Gagne et al16</td>
<td>8 wk</td>
<td>769</td>
<td>Atorvastatin/simvastatin/lovastatin/pravastatin/cerivastatin/fluvastatin–ezetimibe 10 mg</td>
<td>CK ≥10 × ULN with muscle symptoms (statin††)</td>
<td>—</td>
<td>—</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

CK = creatine kinase; CKD = chronic kidney disease; UK-HARP-II = Second United Kingdom Heart and Renal Protection; ULN = upper limit of normal; VYVA = Vytorin Versus Atorvastatin.

* These groups were not related.
† No cases of rhabdomyolysis were reported.
‡ One case of myalgia unassociated with increased CK while taking ezetimibe was reported.
§ No cases of myopathy or rhabdomyolysis were reported.
¶ Myopathy was reported in 1 patient taking ezetimibe.
# Myopathy was reported in 2 patients taking simvastatin.
†† One patient was taking cerivastatin.
* There were no reports of CK >10 × ULN with muscle symptoms.
** Of the 2 patients taking simvastatin, 1 had myopathy. The patient taking simvastatin 40 mg with ezetimibe also had myopathy.
†† One patient was taking cerivastatin.
are glucuronidated by the uridine diphosphate glycosyltransferase 1 family polypeptide A1 enzyme. However, if there is an interaction between ezetimibe and a statin, it is speculative and requires more study. Furthermore, the area under the curve for ezetimibe with statins suggests little or minimal interaction in increasing statin serum levels.4,29

**Does the Use of Cholesterol Absorption Inhibitor Therapy Increase the Risk for Elevations in Liver Transaminases Over What Would Be Experienced With Statins Alone?**

**Response:** Yes.

**Confidence/level of evidence:** 2B (Table 1).

**Rationale:** Ezetimibe has been shown to cause elevations in liver transaminases. Ezetimibe alone, however, does not appear to increase transaminase levels significantly. In controlled clinical monotherapy studies, the incidence of consecutive elevations (≥3 times ULN) in serum transaminases was similar between ezetimibe (0.5%) and placebo (0.3%) (Table 3).1–16 These studies established that mean and median changes from baseline for alanine aminotransferase and, to a lesser extent, aspartate aminotransferase tended to be approximately 1–2 mU/mL greater with ezetimibe than with placebo. Of great importance, there were no significant changes in direct bilirubin levels, the most sensitive marker of drug-induced hepatocellular injury. The increases from baseline in alanine aminotransferase or aspartate aminotransferase activity consist mainly of changes from within the reference ranges to values <2 times upper reference limits and occur often in patients whose baseline values are already greater than the upper limits of the reference ranges. Of the observed alanine aminotransferase activity ≥2 times ULN, most high values are isolated and reversible after treatment discontinuation and sometimes with continued treatment. These elevations in transaminases have not been correlated with any apparent clinical significance (Table 3).1–16 Clinical evidence to date does not associate ezetimibe with concomitant increases in bilirubin levels, jaundice, or symptoms of liver injury, and there has been no association with cholestasis.

The mechanism of action by which ezetimibe may increase liver enzymes is not entirely understood but may represent a secondary effect of changes in lipid metabolism observed with lipid-altering agents, possibly owing to alterations in hepatic metabolism.30–36

**Is There Any Evidence That These Elevations in Liver Transaminases Lead to Liver Failure, Liver Transplantation, or Death Due to Liver Toxicity?**

**Response:** No.

**Confidence/level of evidence:** 2B (Table 1).

There have been no reports of liver failure, liver transplantation, or death due to liver toxicity associated with ezetimibe to date. After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase 2 reaction), with subsequent biliary and renal excretion. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling. In patients with hepatic insufficiency, the bioavailability of ezetimibe has been shown to be increased. After a single 10-mg dose of ezetimibe, the area under the curve for total ezetimibe increased approximately 1.7 times in patients with mild hepatic insufficiency (Child-Pugh score 5–6); the Child-Pugh score is a composite score of bilirubin, serum albumin, international normalized ratio, ascites, and hepatic encephalopathy used to assess the prognosis of chronic liver disease and approximately 3–4 times and 5–6 times, respectively, in those with moderate (Child-Pugh score 7–9) or severe (Child-Pugh score 10–15) hepatic impairment.20 In a 14-day, multiple-dose study (ezetimibe 10 mg/day) in patients with moderate hepatic insufficiency, the mean area under the curve for ezetimibe increased approximately 4-fold on days 1 and 14. Because of the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended in these patients. No dosage adjustment is necessary in patients with mild hepatic insufficiency.

With the coadministration of ezetimibe with a statin, there is increased transaminitis. When ezetimibe is initiated concurrently with a statin, the incidence of consecutive elevations (≥3 times ULN) in serum transaminases was shown to be 1.3% for patients treated with ezetimibe administered with statins compared with 0.4% for patients treated with statins alone5,6,9,11–15,29 (Table 3). The incidence does appear to be dose related with statins and not related to the degree of low-density lipoprotein (LDL) reduction. The data with combination ezetimibe and simvastatin best illustrate the increase in liver transaminases with increasing statin doses. With all combination doses of ezetimibe and simvastatin (from ezetimibe 10-simvastatin 10 to ezetimibe 10-simvastatin 80 mg), the 12-week incidence was 1.7% overall compared with 2.6% for patients treated with the highest dose (ezetimibe 10-simvastatin 80 mg).37 As is the case with ezetimibe monotherapy, all increases in transaminases were unassociated with clinically meaningful symptoms and returned to baseline levels after the discontinuation of therapy or with continued treatment, and, again, no cases of liver failure, liver transplantation, or death have been reported to date.

When ezetimibe is coadministered with a statin, a liver function test should be performed at the initiation of therapy and according to the recommendations of the statin. Specifically for ezetimibe-simvastatin, manufacturer labeling suggests that liver function tests be performed before titration to the ezetimibe 10-simvastatin 80-mg dose and 3 months afterward. The combination of ezetimibe with a statin is contraindicated for patients with active liver disease or unexplained persistent elevations in serum transaminases.29
<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Reported Liver Findings</th>
<th>Placebo</th>
<th>Ezetimibe</th>
<th>Statin</th>
<th>Statin/Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duszynski et al</td>
<td>12 wk</td>
<td>892</td>
<td>Ezetimibe 10 mg</td>
<td>ALT &gt;3×ULN</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Knopp et al</td>
<td>12 wk</td>
<td>827</td>
<td>Ezetimibe 10 mg</td>
<td>AST &gt;3×ULN</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ezetimibe-statin combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe-atorvastatin: Ballantyne et al</td>
<td>12 wk</td>
<td>628</td>
<td>Atorvastatin 10, 20, 40, 80 mg–ezetimibe 10 mg</td>
<td>ALT &gt;3×ULN</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Ezetimibe-atorvastatin: Stein et al</td>
<td>14 wk</td>
<td>621</td>
<td>Atorvastatin 10, 20, 40, 80 mg–ezetimibe 10 mg</td>
<td>ALT and/or AST &gt;3×ULN</td>
<td>—</td>
<td>&lt;1%</td>
<td>—</td>
<td>1%</td>
</tr>
<tr>
<td>Ezetimibe-pravastatin: Melani et al</td>
<td>12 wk</td>
<td>538</td>
<td>Pravastatin 10, 20, 40 mg–ezetimibe 10 mg</td>
<td>ALT &gt;3×ULN</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Davidson et al</td>
<td>12 wk</td>
<td>668</td>
<td>Simvastatin 10, 20, 40, 80 mg–ezetimibe 10 mg</td>
<td>ALT &gt;3×ULN</td>
<td>0%</td>
<td>0%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin (vs atorvastatin): Ballantyne et al</td>
<td>28 wk</td>
<td>788</td>
<td>Simvastatin 10, 20, 40 mg–ezetimibe 10 mg vs atorvastatin 10, 20, 40, 80 mg</td>
<td>ALT &gt;3×ULN</td>
<td>—</td>
<td>—</td>
<td>2.4%</td>
<td>2.3% (10 mg-10 mg); 2.0% (10 mg-20 mg)</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin (vs atorvastatin): VYVA</td>
<td>6 wk</td>
<td>1,902</td>
<td>Simvastatin 10, 20, 40, 80 mg–ezetimibe 10 mg vs atorvastatin 10, 20, 40, 80 mg</td>
<td>ALT &gt;3×ULN</td>
<td>—</td>
<td>—</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Feldman et al</td>
<td>23 wk</td>
<td>710</td>
<td>Simvastatin 10, 20, 40 mg–ezetimibe 10 mg</td>
<td>ALT and/or AST &gt;3×ULN</td>
<td>—</td>
<td>—</td>
<td>4.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Goldberg et al</td>
<td>12 wk</td>
<td>887</td>
<td>Simvastatin 10, 20, 30, 80 mg–ezetimibe 10 mg</td>
<td>ALT and/or AST &gt;3×ULN</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Bays et al</td>
<td>12 wk</td>
<td>1,528</td>
<td>Simvastatin 10, 20, 40 mg–ezetimibe 10 mg</td>
<td>ALT and/or AST &gt;3×ULN</td>
<td>—</td>
<td>—</td>
<td>1.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Ezetimibe-simvastatin: Landray et al (UK-HARP-II) &amp; (patients with CKD)</td>
<td>6 mo</td>
<td>203</td>
<td>Simvastatin 20 mg–ezetimibe 10 mg</td>
<td>ALT 2–3×ULN</td>
<td>—</td>
<td>—</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Ezetimibe added to statin: Gagne et al</td>
<td>8 wk</td>
<td>769</td>
<td>Atorvastatin/simvastatin/lovastatin/pravastatin/cerivastatin/fluvastatin–ezetimibe 10 mg</td>
<td>ALT &gt;3×ULN</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD = chronic kidney disease; GGT = γ-glutamyl transferase; UK-HARP-II = Second United Kingdom Heart and Renal Protection; ULN = upper limit of normal; VYVA = Vytorin (ezetimibe/simvastatin; Merck/Schering-Plough, North Wals, PA) versus atorvastatin.

* Not clinically significant.
† No concomitant increase in bilirubin, jaundice, or symptoms of liver injury were reported.
‡ All elevations in hepatic enzymes were asymptomatic.
§ No cases of hepatitis, jaundice, or other clinical signs of liver dysfunction were reported.
¶ Jaundice did not develop in any subject.
# No patients developed hepatitis or other clinically manifest hepatic adverse events.
** No adverse experiences of hepatitis were reported. One patient had transient illness with elevations of ALT and AST >10 times ULN.
Do Bile Acid Sequestrants Lead to Constipation?

Response: Yes.

Confidence/level of evidence: 1A (Table 1).
Low-density lipoprotein cholesterol reduction with colesvelelam alone, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) alone, and the combination of colesvelelam and a statin

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Colesevelam</th>
<th>Comparison Drug Alone</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>3.8 g/day Alone</td>
<td>−12%</td>
<td>−38%</td>
</tr>
<tr>
<td>Atorvastatin 10 mg/day</td>
<td>−16%</td>
<td>−26%</td>
<td>−42%</td>
</tr>
<tr>
<td>Simvastatin 10 mg/day</td>
<td>−7%</td>
<td>−22%</td>
<td>−34%</td>
</tr>
<tr>
<td>Lovastatin 10 mg/day</td>
<td>−10%</td>
<td>−12%</td>
<td>−16%</td>
</tr>
</tbody>
</table>

Adapted from Atherosclerosis, Am J Med, and Clin Cardiol.

**If Yes, Do Specific Bile Acid Sequestrants Differ in Their Propensity for This Effect?**

Response: Yes.

Confidence/level of evidence: 2C (Table 1).

**Rationale:** BAS have a degree of systemic safety because they are not absorbed from the GI tract into the blood. However, the acceptance of BAS by patients with hypercholesterolemia is diminished by the factors of (1) bulk and palatability, and (2) side effects of bloating and constipation. By the end of the 7-year Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), 27% of men randomized to cholestyramine were taking <2 g/day, despite a goal dose of 24 g/day.

Bowel obstruction with BASs is very rare but has been reported in infants and in a child. The child, who had undergone an appendectomy 3 months previously, developed acute intestinal obstruction requiring laparotomy after taking a total of 8 g of cholestyramine over 2 days.

Colesvelelam, a newer anion exchange polymer specifically designed for the absorption of bile acids, has been suggested to have improved GI tolerance compared with the older BAS resins cholestyramine and colestipol. In a meta-analysis of 3 randomized, placebo-controlled trials of colesvelelam added to statin therapy, constipation was reported by <10% of patients taking colesvelelam, and <5% withdrew from the studies because of medication-related adverse effects. No study has directly compared colesvelelam with an older BAS. However, in LRC-CPPT, 39% of patients taking cholestyramine reported moderate-to-severe constipation in the first year of the study. This is a much higher rate than that reported with the clinical trials of colesvelelam.

Can Bile Acid Sequestrants Potentiate Severe Hypertriglyceridemia?

Response: Yes.

Confidence/level of evidence: 3D (Table 1).

BAS in moderate-to-high doses increase plasma triglyceride levels. BAS should be avoided in patients with high triglycerides (>400 mg/dL [1 mg/dL = 0.01129 mmol/L]), because they tend to increase triglyceride levels. As monotherapy, BAS generally should be used in patients with triglycerides <200 mg/dL.

The Older Bile Acid Sequestrants Colestipol and Cholestyramine Significantly Reduced the Bioavailability of Certain Anionic Drugs, Requiring Them to Be Administered 1 Hour Before or 4 Hours After Administration of the Resins to Avoid or Minimize the Interaction; Should Similar Precautions Be Taken with the Newer Bile Acid Sequestrant Colesvelelam?

Response: No.

Confidence/level of evidence: 2A (Table 1).

Rationale: Colestipol and cholestyramine are insoluble, high-molecular weight, basic anion exchange copolymer resins that bind with bile acids in the GI tract to form a complex that is excreted in the feces. By this action, enterohepatic circulation of bile acids is reduced, prompting hepatic cholesterol to be converted by the action of 7α-hydroxylase into bile acids for secretion into the bile and to upregulate hepatic LDL receptors to enhance the removal of LDL cholesterol from the systemic circulation. By a similar action, these bile acid resins have been shown to bind to a number of coadministered drugs, resulting in a significant reduction in their absorption and biologic activity. Drugs affected by this interference include statins, thiazide diuretics, furosemide, spironolactone, ezetimibe, fenofibrate, tricyclic antidepressants, oral corticosteroids, dicyclocam, digoxin, some sulfonylureas, thyroid hormones, phenobarbital, vitamin K, raloxifene, loperamide, and some nonsteroidal anti-inflammatory agents.

Colesvelelam acts in a similar fashion, binding with bile acids in the GI tract, interrupting their enterohepatic circulation, causing more hepatic cholesterol to be converted to bile acids, and increasing the uptake of LDL particles via the upregulated LDL receptor on the surface of the hepatocyte. What is unique about colesvelelam is that its polymer structure allows for enhanced specificity, greater affinity, and higher binding strength with bile acids. Because of the high affinity of binding sites for bile acids, access of other molecules to these sites is limited. Thus, on a conceptual basis, reduced bioavailability because of the GI binding of coadministered drugs should be less of a problem with colesvelelam.

Drug interaction studies with colesvelelam have been conducted in normal, healthy subjects who receive single doses of the test drug either alone or in combination with colesvelelam. In these studies, the area under the time-concentration curve as well as the peak concentrations achieved of the test drugs were compared. The study results revealed no change in the bioavailability of digoxin, warfarin, valproic acid, quinidine, metoprolol, fenofibrate,
or lovastatin. No data are available on potential interactions with thyroid hormones.

Pharmacodynamic studies have been carried out with multiple doses of a number of statins alone or with colesevelam in patients with hypercholesterolemia.51-53 If colesevelam significantly interfered with the bioavailability of a statin, one would expect to see a diminution in LDL cholesterol lowering. In 3 studies of similar design (each testing the initial dose of a different statin), enhanced, additive LDL cholesterol lowering was demonstrated when colesevelam was added to the statins (Table 5).51-53 A similar additive effect has also been demonstrated with colesevelam-fenofibrate and colesevelam-ezetimibe combination regimens.54-55 Thus, neither single-dose pharmacokinetic nor multiple-dose pharmacodynamic studies have demonstrated a significant interaction when colesevelam is used in combination with commonly used concurrent therapies.

Final Conclusions and Recommendations for Bile Acid Sequestrants

The recommendations for healthcare providers regarding BAS safety are summarized in Table 6.

Table 6

Recommendations to healthcare professionals regarding the safety of bile acid sequestrants (BAS)

1. BAS are known to produce or worsen constipation. Patients prone to constipation will likely do better with colesevelam than with either cholestyramine or colestipol. BAS should be avoided in patients with disorders involving low motility of the small or large intestine, in patients with recent abdominal surgery, and in patients with recent or repeated episodes of intestinal obstruction. BAS are contraindicated in patients with complete biliary obstruction, in which bile is not secreted into the intestine.

2. BAS should be avoided in patients with high triglyceride levels (≥400 mg/dL) because they tend to raise triglyceride levels. As monotherapy, BAS generally should be used in patients with triglyceride levels <200 mg/dL. Patients with hypertriglyceridemia should have triglyceride levels monitored periodically while taking BAS.

3. Anionic drugs such as phenylbutazone, warfarin, thiazide diuretics, or propanolol, as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens, progestins, and digitals, should be administered 1 hour before or 4 hours after (or at least as great an interval as possible) administration of the older BAS colestipol and cholestyramine to avoid significantly interfering with their bioavailability. On the basis of the evidence available to date, the newer BAS colesevelam can be administered concurrently with other drugs. There are, however, no drug interaction data available for colesevelam and thyroid hormone preparations, although the other BAS are known to decrease their absorption.


Expert Commentary: Gastrointestinally Active Lipid-Lowering Drug Safety

Peter P. Toth, MD, PhD

Atherosclerosis is a widely prevalent, insidious disease that causes acute coronary syndromes (ACS), intermittent claudication, ischemic stroke, and a high percentage of sudden deaths, among other complications. Given the well-known observations that populations worldwide are living longer, that more patients are surviving ACS, and that there are evolving epidemics of obesity, metabolic syndrome, and diabetes mellitus encompassing the globe, the number of patients expected to be afflicted by atherosclerotic disease continues to escalate precipitously. Both sexes and all racial and ethnic groups are at risk for the development of atherosclerotic disease, with some disproportionately so. Managing a patient’s global cardiovascular risk burden through a combination of lifestyle modification and pharmacologic intervention is crucial to any effort directed at reducing risk for cardiovascular morbidity and mortality. An internal milieu favoring the development of a proinflammatory, prooxidative, and prothrombotic state, in conjunction with derangements in lipoprotein metabolism, promotes arterial wall remodeling and atheromatous lesion development and progression.

Lipid-lowering therapy is an evidence-based, highly validated approach to risk reduction in the primary and secondary prevention settings. Although currently available lipid-lowering agents have been shown to have acceptable benefit-to-risk ratios in men and women, significant concern continues regarding the safety of these agents. A patient’s safety must always be a healthcare provider’s highest responsibility. Concerns about risk and benefit must be weighed not only in populations but in each patient. Physicians should take into account factors such as hepatic or renal impairment, age, history of medication-induced adverse events, the potential for drug interactions, and unforeseen idiosyncratic reactions potentiated by highly individual genetic and metabolic backgrounds. The need for vigilance and a timely response to a patient’s concerns is intrinsic to any plan of care. It is recognized that every form of therapy has some risks for adverse events, and these risks always should be explained to patients in context.

However, significant effort must be expended to ensure that the risk for adverse events in patients treated with lipid-lowering therapy is not exaggerated. The role of lipid-lowering therapy in patients at risk for an ACS is among the most intensively studied areas in all of medicine. Yet misinformation in media coverage and inflammatory positions espoused by a variety of patient “advocacy groups” frequently frustrate our best efforts to treat dyslipidemias optimally. By suggesting that drugs are inherently dangerous, much of this activity actually endangers patients and leaves them at excessive risk for first-time and recurrent events, including death. The health-supplements industry makes claims about the efficacy of herbal and organic agents in the absence of rigorous evidence. Unfortunately, because many patients believe that an “organic approach” is healthier and safer than pharmacologic intervention, they opt for the former. Chelation is another example of this. Physicians and midlevel providers must do more to counterbalance this negativity and actively promote the lifesaving benefits and reduced suffering that prescription lipid-lowering agents offer.

Although adverse event reporting encompasses every type of systemic reaction and symptom clinically describable, the 2 most important adverse events attributable to antilipidemic agents are liver toxicity and myopathy (including rhabdomyolysis). Rhabdomyolysis is likely the most important manifestation of toxicity and has the highest rate of mortality, especially if not recognized early. Although speculation abounds, the precise cause of liver and skeletal muscle toxicity are as yet inadequately understood. Alterations in isoprenoid metabolism, changes in cell membrane cholesterol content and fluidity, impaired mitochondrial electron transport and rates of oxidative phosphorylation (possibly through reduced coenzyme Q or cytochrome oxidase activity), increases in intrahepatic and intramyocellular triglyceride content, and alterations in intracellular signaling pathways have all been implicated. Polymorphisms in cytochrome P450 (CYP) isozymes and glucuronosyltransferases may also give rise to increased risk for impaired metabolism and drug toxicity. Lipid-lowering agent–induced transaminitis and skeletal muscle toxicity are real phenomena. However, adverse event reporting must be juxtaposed to a number of clinical realities. First, myalgias are quite common, and just because a patient is taking a lipid-lowering agent does not, of necessity, directly implicate the drug as the source of toxicity. Second, creatine kinase elevations can be caused by injuries so minor that a patient may not even recall subtle muscle trauma that may increase enzyme levels by 2-fold to 5-fold compared with baseline. In at least some cases, previously undetected, established muscle disease also undoubtedly contributes to this increase. Third, transaminase levels fluctuate. If a pa-
nitis or myopathy is consistently not significantly different from that with placebo or, in patients receiving combination therapy, statin monotherapy. Transaminase elevations, when they occur, tend to be transient and not associated with hepatotoxicity. Persistent transaminase elevations have been shown to be reversible when ezetimibe therapy is withdrawn. There is no apparent signal for GI toxicity, and ezetimibe does not precipitate diarrhea. In addition, ezetimibe significantly increases the reductions in C-reactive protein observed with statin therapy.

Multiple prospective trials evaluating this medication’s capacity to augment cardiovascular risk reduction by statin therapy are under way. Additional cholesterol absorption blockers also are in development.

Bile acid sequestrants (BAS) are anion-exchange resins that bind bile acids in the intestinal lumen. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPP), cholestyramine therapy given to men with established coronary artery disease (CAD) was associated with a significant 19% reduction in nonfatal myocardial infarction and CAD-related mortality. BAS therapy is also associated with reduced rates of progression of CAD compared with placebo. Cholestyramine and colestipol are generally ingested as slurries mixed in juices. A third BAS is colesevelam, which is taken as a pill. BAS are not hydrolyzed by digestive enzymes and are not systemically absorbed. By reducing bile acid reabsorption via the ileal bile acid–sodium cotransporter, there is increased demand for de novo synthesis of bile acids by hepatocytes. BAS therapy is associated with increased expression of the LDL receptor and augmented systemic clearance of LDL cholesterol, as well as increased activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step for cholesterol biosynthesis. The cholesterol is then converted to cholate and chenodeoxycholate via the activity of 7α-hydroxylase. BAS are associated with dose-dependent reductions in LDL cholesterol (10%–30%) and increases in HDL cholesterol. BAS should be used with caution in patients with hypertriglyceridemia, because their use can be associated with elevations in serum triglycerides, although this appears to be less of a concern with colesevelam. There is some evidence that BAS therapy can activate liver X receptor–α, which in turn may lead to the coordinated activation of the enzymatic machinery necessary for triglyceride biosynthesis (eg, fatty acid synthase, acetyl coenzyme A carboxylase, and stearoyl coenzyme A desaturase–1).

BAS therapy is not associated with significant elevations in serum hepatic transaminase levels, and because BAS are nonsystemic agents, they do not increase risk for hepatotoxicity or myopathy. There is no need to monitor liver function tests with BAS monotherapy. BAS do not adversely affect CYP-dependent drug metabolism; however, BAS administered in powdered form (cholestyramine, colestipol) can reduce the absorption of a number of drugs, such as digoxin, thyroxine, and propranolol, among others. Colesevelam can reduce the absorption of sustained-release
Consequently, other medications should be given 1 hour before, or 4–6 hours after, the ingestion of BAS. BAS are safe to use in combination with statins\textsuperscript{17,18} or ezetimibe\textsuperscript{19} and provide additive changes in LDL cholesterol and HDL cholesterol. The most frequently cited adverse reactions with BAS are GI related, including constipation, flatulence, and dyspepsia. Some BAS have been available for >3 decades, with no apparent signal for toxicity that would preclude their use in patients able to tolerate their GI side effects. Colesevelam has a more favorable GI side effect profile compared with other currently available resins.\textsuperscript{20}

Ezetimibe and BAS have consistently demonstrated acceptable safety profiles and induce favorable changes in LDL cholesterol and HDL cholesterol when used as either monotherapy or in combination with statins. These drugs have an important role to play when managing patients with dyslipidemia, especially when statin monotherapy reduces atherogenic lipoproteins inadequately or when statins are not well tolerated or there is resistance to their titration. These drugs also provide the opportunity to affect lipid metabolism beneficially through multiple, clinically meaningful mechanisms and biosynthetic pathways. It is anticipated that as more polymorphisms in the genes for 7α-hydroxylase and NPC1L1 protein are discovered, the therapeutic role of these agents will expand.


NOTES
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